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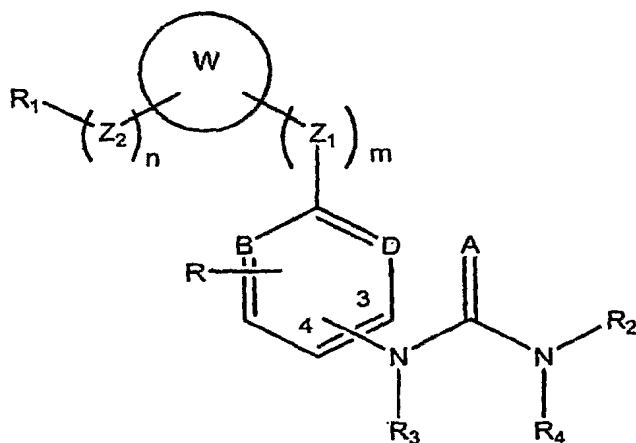
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(54) Title: 1,3 SUBSTITUTED DIARYL UREAS AS MODULATORS OF KINASE ACTIVITY



(1)

(57) Abstract: Certain chemical entities chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, are provided herein. Pharmaceutical compositions comprising at least one chemical entity and one or more pharmaceutically acceptable vehicle chosen from carriers, adjuvants, and excipients, are also provided herein. Use in treating patients suffering from certain diseases and disorders responsive to angiogenic kinase modulation, which comprise administering to such patients an amount of at least one chemical entity effective to reduce signs or symptoms of the disease or disorder are disclosed. These diseases include cancer, including breast neoplasia, endometrial cancer, colon cancer, and neck squamous cell carcinoma. A method for determining the presence or absence of an angiogenic kinase in a sample comprising contacting the sample with at least one chemical entity

under conditions that permit detection of activity of the angiogenic kinase, detecting a level of the activity of the angiogenic kinase, and therefrom

1,3 SUBSTITUTED DIARYL UREAS AS MODULATORS OF KINASE ACTIVITY

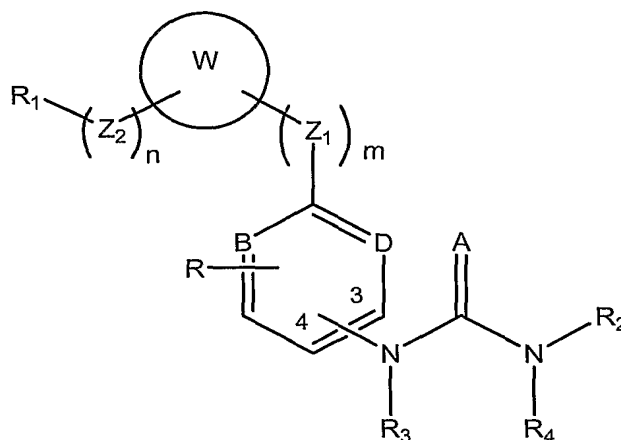
[0001] This application claims priority to U.S. Provisional Application No. 60/643,856, filed January 14, 2005, and U.S. Provisional Application No. 60/733,116, filed November 2, 2005. Each of those applications is incorporated herein by reference.

[0002] Provided herein are certain substituted ureas and related compounds, compositions comprising such compounds, and methods of their use.

[0003] Protein kinases, the largest family of human enzymes, encompass well over 500 proteins. Kinases play a key role in angiogenesis. Angiogenesis, the formation of new blood vessels from preexisting ones, plays a significant role in many pathological settings, including cancer, chronic inflammation, diabetic retinopathy, psoriasis, rheumatoid arthritis, and macular degeneration. Anti-angiogenic therapy represents a potentially important approach for the treatment of solid tumors and other diseases associated with dysregulated vascularization.

[0004] The process of angiogenesis is complex, requiring the concerted actions of multiple angiogenic mediators as well as the participation of different cell types. Key angiogenesis mediators, including, VEGF, FGF, and angiopoietin 1 and 2 (Ang1 and Ang2) that bind to their cognate receptors (VEGFRs, FGFRs and Tie1 and Tie2, respectively) expressed on endothelial cells, as well as platelet-derived growth factor (PDGF) that binds to its receptor (PDGFR α) expressed on VEGF-producing stromal cells or its receptor (PDGFR β) expressed on pericytes and smooth muscle cells have been identified. Recent studies indicate that several members of the ephrin family and their receptor Eph family are also regulators of angiogenesis. VEGFRs, FGFRs, Tie1, Tie2, PDGFRs, and Eph receptors all belong to the receptor protein tyrosin kinase (RTK) superfamily. Given the important roles of these RTKs in angiogenesis, their modulation would be pharmacologically desirable for the treatment of cancer and other diseases associated with dysregulated vascularization.

[0005] Provided is at least one chemical entity chosen from compounds of Formula 1



(Formula 1)

and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, wherein

A is chosen from O and S;

B and D are chosen from CH and N, provided that at least one of B and D is CH;

R represents 0 to 2 substituents independently chosen from hydroxy, nitro, cyano, optionally substituted amino, aminocarbonyl, halo, carboxy, optionally substituted acyl, optionally substituted alkoxy, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, sulfanyl, sulfinyl, sulfonyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycloalkyl;

R₁ is optionally substituted heteroaryl;

W is optionally substituted heteroaryl;

Z₁ is -CR₅R₆- wherein each R₅ and R₆ is independently chosen from hydrogen, optionally substituted C₁-C₆ alkyl, and halo;

m is chosen from 0, 1, and 2;

Z₂ is -CR₇R₈- wherein each R₇ and R₈ is independently chosen from hydrogen, optionally substituted C₁-C₆ alkyl, and halo;

n is chosen from 0, 1, and 2;

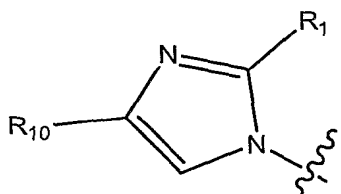
R₂ is optionally substituted aryl; and

R₃ and R₄ are each independently chosen from hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted aryl, and optionally substituted heteroaryl,

provided that

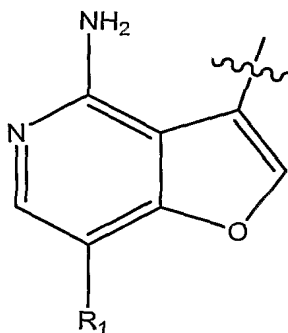
R₁ is not 4-aminothieno[2,3-d]pyrimidine-6-yl when n is 0, m is 0, W is 1-methyl-1H-imidazol-4,5-diyl, A is CH, R is absent, R₃ and R₄ are hydrogen, and R₂ is chosen from phenyl and 2-fluoro-5-(trifluoromethyl)phenyl;

when n is 0, m is 0, A is CH, and R is absent, W is not



where R₁₀ is chosen from CF₃, halo; CN, C₁-C₈ alkyl, C₁-C₆ alkenyl; C₃-C₈ cycloalkyl optionally substituted with a group chosen from hydroxy, cyano, and methoxy, C₁-C₈ alkoxy; C₁-C₄ alkyloxyalkyl; C₁-C₈ alkylthio; C₁-C₄ alkylthioalkyl; C₁-C₈ dialkylamino; C₁-C₄ dialkylaminoalkyl; alkoxycarbonyl optionally substituted with a group chosen from carbocyclyl and heterocyclyl; aryl and heterocyclyl, wherein the aryl and heterocyclyl groups may be optionally substituted with a group chosen from halo, C₁-C₄ alkyl, C₁-C₄ alkenyl, CN, dimethylamino, methoxycarbonyl, methoxy, aryl, and heterocyclyl;

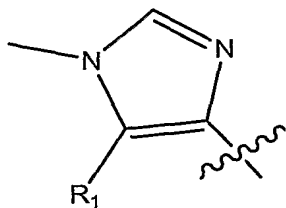
when n is 0, m is 0, A is CH, R is absent, and R₂ is 2-fluoro-5-trifluoromethylphenyl,



W is not

where R₁ is pyridin-3-yl; and

when n is 0, m is 0, A is CH, R is absent, and R₂ is chosen from phenyl and 2-fluoro-5-(trifluoromethyl)phenyl, W is not



where R₁ is 4-aminoethieno[2,3-d]pyrimidin-6-yl.

[0006] In certain embodiments, at least one chemical entity exhibits an IC₅₀ of 1 micromolar or less in a standard *in vitro* assay of EphB₄ kinase activity.

[0007] In certain embodiments, at least one chemical entity exhibits an IC₅₀ of 1 micromolar or less in a standard *in vitro* assay of c-Kit kinase activity.

[0008] In certain embodiments, at least one chemical entity exhibits an IC₅₀ of 1 micromolar or less in a standard *in vitro* assay of VEGFR2 kinase activity.

[0009] In certain embodiments, at least one chemical entity exhibits an IC₅₀ of 1 micromolar or less in standard *in vitro* assay of Tie2 kinase activity.

[0010] Also provided is a pharmaceutical composition, comprising at least one chemical entity described herein, together with at least one pharmaceutically acceptable vehicle chosen from carriers, adjuvants, and excipients. Also provided is a packaged pharmaceutical composition, comprising the pharmaceutical composition in a container; and instructions for using the composition to treat a patient suffering from a disease or disorder responsive to kinase activity modulation of one or more tyrosine kinase.

[0011] Also provided is a method of treating a patient having a disease or disorder responsive to kinase activity modulation comprising administering to the patient a therapeutically effective amount of at least one chemical entity described herein.

[0012] Also provided is a method for treating a female patient having a female reproductive disorder or condition comprising administering to the female patient a therapeutically effective amount of at least one chemical entity described herein or a pharmaceutical composition described herein.

[0013] Also provided is a method of modulating EphB₄ kinase activity comprising contacting cells expressing EphB₄ with at least one chemical entity described herein in an amount sufficient to detectably inhibit EphB₄ kinase activity *in vitro*.

[0014] Also provided is a method of modulating VEGFR2 kinase activity comprising contacting cells expressing VEGFR2 with at least one chemical entity described herein in an amount sufficient to detectably inhibit VEGFR2 kinase activity *in vitro*.

[0015] Also provided is a method of modulating c-Kit kinase activity comprising contacting cells expressing c-Kit with at least one chemical entity described herein in an amount sufficient to detectably inhibit c-Kit kinase activity *in vitro*.

[0016] Also provided is a method of modulating Tie2 kinase activity comprising contacting cells expressing Tie2 with at least one chemical entity described herein in an amount sufficient to detectably inhibit Tie2 kinase activity *in vitro*.

[0017] Also provided is a method of modulating an activity of at least one kinase chosen from VEGFR2, EphB₄, Tie2, and c-Kit, the method comprising contacting cells expressing at least one kinase chosen from VEGFR2, EphB₄, Tie2, and c-Kit with at least one chemical entity described herein in an amount sufficient to detectably inhibit the activity of at least one kinase chosen from VEGFR2, EphB₄, Tie2, and c-Kit *in vitro*.

[0018] Also provided is the use of at least one chemical entity described herein for the manufacture of a medicament for the treatment of a patient having a disease or disorder

responsive to activity modulation of at least one kinase chosen from VEGFR2, EphB₄, Tie2, and c-Kit kinase.

[0019] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0020] Formula 1 includes all subformulae thereof. For example Formula 1 includes compounds of Formulae 1 to 4.

[0021] As used herein, when any variable occurs more than one time in a chemical formula, its definition on each occurrence is independent of its definition at every other occurrence. In accordance with the usual meaning of “a” and “the” in patents, reference, for example, to “a” kinase or “the” kinase is inclusive of one or more kinases.

[0022] A dash (“-”) that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -CONH₂ is attached through the carbon atom.

[0023] By “optional” or “optionally” is meant that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, “optionally substituted alkyl” encompasses both “alkyl” and “substituted alkyl” as defined below. It will be understood by those skilled in the art, with respect to any group containing one or more substituents, that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical, synthetically non-feasible and/or inherently unstable.

[0024] “Alkyl” encompasses straight chain and branched chain having the indicated number of carbon atoms, usually from 1 to 20 carbon atoms, for example 1 to 8 carbon atoms, such as 1 to 6 carbon atoms. For example C₁-C₆ alkyl encompasses both straight and branched chain alkyl of from 1 to 6 carbon atoms. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, 3-methylpentyl, and the like. Alkylene is another subset of alkyl, referring to the same residues as alkyl, but having two points of attachment. Alkylene groups will usually have from 2 to 20 carbon atoms, for example 2 to 8 carbon atoms, such as from 2 to 6 carbon atoms. For example, C₀ alkylene indicates a covalent bond and C₁ alkylene is a methylene group. When an alkyl residue having a specific number of carbons is named, all geometric combinations having that number of carbons are intended to be encompassed; thus, for example, “butyl” is meant to include n-butyl, sec-butyl, isobutyl and t-butyl;

"propyl" includes n-propyl and isopropyl. "Lower alkyl" refers to alkyl groups having one to four carbons.

[0025] "Alkenyl" refers to an unsaturated branched or straight-chain alkyl group having at least one carbon-carbon double bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkene. The group may be in either the *cis* or *trans* conformation about the double bond(s). Typical alkenyl groups include, but are not limited to, ethenyl; propenyls such as prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl), prop-2-en-2-yl, cycloprop-1-en-1-yl; cycloprop-2-en-1-yl; butenyls such as but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl; and the like. In certain embodiments, an alkenyl group has from 2 to 20 carbon atoms and in other embodiments, from 2 to 6 carbon atoms.

[0026] "Alkynyl" refers to an unsaturated branched or straight-chain alkyl group having at least one carbon-carbon triple bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkyne. Typical alkynyl groups include, but are not limited to, ethynyl; propynyls such as prop-1-yn-1-yl, prop-2-yn-1-yl; butynyls such as but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl; and the like. In certain embodiments, an alkynyl group has from 2 to 20 carbon atoms and in other embodiments, from 3 to 6 carbon atoms.

[0027] "Cycloalkyl" indicates a non-aromatic carbocyclic ring, usually having from 3 to 7 ring carbon atoms. The ring may be saturated or have one or more carbon-carbon double bonds. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, and cyclohexenyl, as well as bridged and caged saturated ring groups such as norbornane.

[0028] By "alkoxy" is meant an alkyl group of the indicated number of carbon atoms attached through an oxygen bridge such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentyloxy, 2-pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, 2-hexyloxy, 3-hexyloxy, 3-methylpentyloxy, and the like. Alkoxy groups will usually have from 1 to 6 carbon atoms attached through the oxygen bridge. "Lower alkoxy" refers to alkoxy groups having one to four carbons.

[0029] "Mono- and di-alkylcarboxamide" encompasses a group of the formula $-(C=O)NR_aR_b$ where R_a and R_b are independently chosen from hydrogen and alkyl groups of the indicated number of carbon atoms, provided that R_a and R_b are not both hydrogen.

[0030] "Acy" refers to the groups (alkyl)-C(O)-; (cycloalkyl)-C(O)-; (aryl)-C(O)-; (heteroaryl)-C(O)-; and (heterocycloalkyl)-C(O)-, wherein the group is attached to the parent

structure through the carbonyl functionality and wherein alkyl, cycloalkyl, aryl, heteroaryl, and heterocycloalkyl are as described herein. Acyl groups have the indicated number of carbon atoms, with the carbon of the keto group being included in the numbered carbon atoms. For example a C₂ acyl group is an acetyl group having the formula CH₃(C=O)-.

[0031] By “alkoxycarbonyl” is meant a group of the formula (alkoxy)(C=O)- attached through the carbonyl carbon wherein the alkoxy group has the indicated number of carbon atoms. Thus a C₁-C₆ alkoxycarbonyl group is an alkoxy group having from 1 to 6 carbon atoms attached through its oxygen to a carbonyl linker.

[0032] By “amino” is meant the group -NH₂.

[0033] “Mono- and di-(alkyl)amino” encompasses secondary and tertiary alkyl amino groups, wherein the alkyl groups are as defined above and have the indicated number of carbon atoms. The point of attachment of the alkylamino group is on the nitrogen. Examples of mono- and di-alkylamino groups include ethylamino, dimethylamino, and methyl-propyl-amino.

[0034] By “amino(alkyl)” is meant an amino group linked to an alkyl group having the indicated number of carbons. Similarly “hydroxyalkyl” is a hydroxy group linked to an alkyl group.

[0035] The term “aminocarbonyl” refers to the group -CONR^bR^c, where

R^b is chosen from H, optionally substituted C₁-C₆ alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl; and

R^c is independently chosen from hydrogen and optionally substituted C₁-C₄ alkyl; or

R^b and R^c taken together with the nitrogen to which they are bound, form an optionally substituted 5- to 7-membered nitrogen-containing heterocycloalkyl which optionally includes 1 or 2 additional heteroatoms selected from O, N, and S in the heterocycloalkyl ring;

where each substituted group is independently substituted with one or more substituents independently selected from C₁-C₄ alkyl, aryl, heteroaryl, aryl-C₁-C₄ alkyl-, heteroaryl-C₁-C₄ alkyl-, C₁-C₄ haloalkyl-, -OC₁-C₄ alkyl, -OC₁-C₄ alkylphenyl, -C₁-C₄ alkyl-OH, -OC₁-C₄ haloalkyl, halo, -OH, -NH₂, -C₁-C₄ alkyl-NH₂, -N(C₁-C₄ alkyl)(C₁-C₄ alkyl), -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)(C₁-C₄ alkylphenyl), -NH(C₁-C₄ alkylphenyl), cyano, nitro, oxo (as a substituent for cycloalkyl, heterocycloalkyl, or heteroaryl), -CO₂H, -C(O)OC₁-C₄ alkyl, -CON(C₁-C₄ alkyl)(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CONH₂, -NHC(O)(C₁-C₄ alkyl), -NHC(O)(phenyl),

-N(C₁-C₄ alkyl)C(O)(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)C(O)(phenyl), -C(O)C₁-C₄ alkyl, -C(O)C₁-C₄ alkylphenyl, -C(O)C₁-C₄ haloalkyl, -OC(O)C₁-C₄ alkyl, -SO₂(C₁-C₄ alkyl), -SO₂(phenyl), -SO₂(C₁-C₄ haloalkyl), -SO₂NH₂, -SO₂NH(C₁-C₄ alkyl), -SO₂NH(phenyl), -NHSO₂(C₁-C₄ alkyl), -NHSO₂(phenyl), and -NHSO₂(C₁-C₄ haloalkyl).

[0036] “Aryl” encompasses:

6-membered carbocyclic aromatic rings, for example, benzene;

bicyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, naphthalene, indane, and tetralin; and

tricyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, fluorene.

Aryl includes 6-membered carbocyclic aromatic rings fused to a 5- to 7-membered heterocycloalkyl ring containing 1 or more heteroatoms chosen from N, O, and S. For example, aryl includes phenyl substituted with -O(C₁-C₂ alkyl)O- (e.g., phenyl substituted with a methylenedioxy or ethylenedioxy group). For such fused, bicyclic ring systems wherein only one of the rings is a carbocyclic aromatic ring, the point of attachment may be at the carbocyclic aromatic ring or the heterocycloalkyl ring. Bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. Bivalent radicals derived from univalent polycyclic hydrocarbon radicals whose names end in “-yl” by removal of one hydrogen atom from the carbon atom with the free valence are named by adding “-idene” to the name of the corresponding univalent radical, e.g., a naphthyl group with two points of attachment is termed naphthylidene. Aryl, however, does not encompass or overlap in any way with heteroaryl, separately defined below. Hence, if one or more carbocyclic aromatic rings is fused with a heterocycloalkyl aromatic ring, the resulting ring system is heteroaryl, not aryl, as defined herein.

[0037] The term “aryloxy” refers to the group -O-aryl.

[0038] The term “halo” includes fluoro, chloro, bromo, and iodo, and the term “halogen” includes fluorine, chlorine, bromine, and iodine.

[0039] “Haloalkyl” indicates alkyl as defined above having the specified number of carbon atoms, substituted with 1 or more halogen atoms, generally up to the maximum allowable number of halogen atoms. Examples of haloalkyl include, but are not limited to, trifluoromethyl, difluoromethyl, 2-fluoroethyl, and penta-fluoroethyl.

[0040] “Heteroaryl” encompasses:

5- to 7-membered aromatic, monocyclic rings containing one or more, for example, from 1 to 4, or in certain embodiments, from 1 to 3, heteroatoms chosen from N, O, and S, with the remaining ring atoms being carbon; and bicyclic heterocycloalkyl rings containing one or more, for example, from 1 to 4, or in certain embodiments, from 1 to 3, heteroatoms chosen from N, O, and S, with the remaining ring atoms being carbon and wherein at least one heteroatom is present in an aromatic ring.

Heteroaryl includes a 5- to 7-membered heterocycloalkyl, aromatic ring fused to a 5- to 7-membered cycloalkyl or heterocycloalkyl ring. For example, heteroaryl includes pyridinyl substituted with -O(C₁-C₂ alkyl)O- (e.g., pyridinyl substituted with a methylenedioxy or ethylenedioxy group). For such fused, bicyclic heteroaryl ring systems, the point of attachment may be at either ring. When the total number of S and O atoms in the heteroaryl group exceeds 1, those heteroatoms are not adjacent to one another. In certain embodiments, the total number of S and O atoms in the heteroaryl group is not more than 2. In certain embodiments, the total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of heteroaryl groups include, but are not limited to, (as numbered from the linkage position assigned priority 1), 2-pyridyl, 3-pyridyl, 4-pyridyl, 2,3-pyrazinyl, 3,4-pyrazinyl, 2,4-pyrimidinyl, 3,5-pyrimidinyl, 2,3-pyrazolinyl, 2,4-imidazolinyl, isoxazolinyl, oxazolinyl, thiazolinyl, thiadiazolinyl, tetrazolyl, thienyl, benzothiophenyl, furanyl, benzofuranyl, benzoimidazolinyl, indolyl, pyridazinyl, triazolyl, quinolyl, pyrazolyl, and 5,6,7,8-tetrahydroisoquinoline. Bivalent radicals derived from univalent heteroaryl radicals whose names end in "-yl" by removal of one hydrogen atom from the atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, e.g., a pyridyl group with two points of attachment is a pyridylidene. Heteroaryl does not encompass or overlap with aryl, cycloalkyl, or heterocycloalkyl, as defined herein

[0041] Substituted heteroaryl also includes ring systems substituted with one or more oxide (-O⁻) substituents, such as pyridinyl N-oxides.

[0042] In the term "heteroarylalkyl," heteroaryl and alkyl are as defined herein, and the point of attachment is on the alkyl group. This term encompasses, but is not limited to, pyridylmethyl, thiophenylmethyl, and (pyrrolyl)1-ethyl.

[0043] By "heterocycloalkyl" is meant a single, non-aromatic ring, usually with 3 to 7 ring atoms, containing at least 2 carbon atoms in addition to 1-3 heteroatoms independently selected from oxygen, sulfur, and nitrogen, as well as combinations comprising at least one of the foregoing heteroatoms. The ring may be saturated or have one or more carbon-carbon

double bonds. Suitable heterocycloalkyl groups include, for example (as numbered from the linkage position assigned priority 1), 2-pyrrolinyl, 2,4-imidazolidinyl, 2,3-pyrazolidinyl, 2-piperidyl, 3-piperidyl, 4-piperidyl, and 2,5-piperziny. Morpholinyl groups are also contemplated, including 2-morpholinyl and 3-morpholinyl (numbered wherein the oxygen is assigned priority 1). Substituted heterocycloalkyl also includes ring systems substituted with one or more oxo (=O) or oxide (-O⁻) substituents, such as piperidinyl N-oxide, morpholinyl-N-oxide, 1-oxo-1-thiomorpholinyl and 1,1-dioxo-1-thiomorpholinyl.

[0044] "Heterocycloalkyl" also includes bicyclic ring systems wherein one non-aromatic ring, usually with 3 to 7 ring atoms, contains at least 2 carbon atoms in addition to 1-3 heteroatoms independently selected from oxygen, sulfur, and nitrogen, as well as combinations comprising at least one of the foregoing heteroatoms; and the other ring, usually with 3 to 7 ring atoms, optionally contains 1-3 heteroatoms independently selected from oxygen, sulfur, and nitrogen and is not-aromatic.

[0045] As used herein, "modulation" refers to a change in kinase activity as a direct or indirect response to the presence of compounds of Formula 1, relative to the activity of the kinase in the absence of the compound. The change may be an increase in activity or a decrease in activity, and may be due to the direct interaction of the compound with the kinase, or due to the interaction of the compound with one or more other factors that in turn affect kinase activity. For example, the presence of the compound may, for example, increase or decrease kinase activity by directly binding to the kinase, by causing (directly or indirectly) another factor to increase or decrease the kinase activity, or by (directly or indirectly) increasing or decreasing the amount of kinase present in the cell or organism.

[0046] The term "sulfanyl" includes the groups: -S-(optionally substituted (C₁-C₆)alkyl), -S-(optionally substituted aryl), -S-(optionally substituted heteroaryl), and -S-(optionally substituted heterocycloalkyl). Hence, sulfanyl includes the group C₁-C₆ alkylsulfanyl.

[0047] The term "sulfinyl" includes the groups: -S(O)-(optionally substituted (C₁-C₆)alkyl), -S(O)-optionally substituted aryl, -S(O)-optionally substituted heteroaryl), -S(O)-(optionally substituted heterocycloalkyl); and -S(O)-(optionally substituted amino).

[0048] The term "sulfonyl" includes the groups: -S(O₂)-(optionally substituted (C₁-C₆)alkyl), -S(O₂)-optionally substituted aryl, -S(O₂)-optionally substituted heteroaryl), -S(O₂)-(optionally substituted heterocycloalkyl), -S(O₂)-(optionally substituted alkoxy), -S(O₂)-optionally substituted aryloxy, -S(O₂)-optionally substituted heteroaryloxy), -S(O₂)-(optionally substituted heterocycloxy); and -S(O₂)-(optionally substituted amino).

[0049] The term “substituted”, as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded. When a substituent is oxo (i.e., =O) then 2 hydrogens on the atom are replaced. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates. A stable compound or stable structure is meant to imply a compound that is sufficiently robust to survive isolation from a reaction mixture, and subsequent formulation as an agent having at least practical utility. Unless otherwise specified, substituents are named into the core structure. For example, it is to be understood that when (cycloalkyl)alkyl is listed as a possible substituent, the point of attachment of this substituent to the core structure is in the alkyl portion.

[0050] The terms “substituted” alkyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl, unless otherwise expressly defined, refer respectively to alkyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl wherein one or more (such as up to 5, for example, up to 3) hydrogen atoms are replaced by a substituent independently chosen from:

-R^a, -OR^b, -SR^b, guanidine, guanidine wherein one or more of the guanidine hydrogens are replaced with a lower-alkyl group, -NR^bR^c, halo, cyano, nitro, oxo (as a substituent for cycloalkyl, heterocycloalkyl, and heteroaryl), -COR^b, -CO₂R^b, -CONR^bR^c, -OCOR^b, -OCO₂R^a, -OCONR^bR^c, -NR^cCOR^b, -NR^cCO₂R^a, -NR^cCONR^bR^c, -CO₂R^b, -CONR^bR^c, -NR^cCOR^b, -SOR^a, -SO₂R^a, -SO₂NR^bR^c, and -NR^cSO₂R^a,

where R^a is chosen from optionally substituted C₁-C₆ alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^b is chosen from H, optionally substituted C₁-C₆ alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl; and

R^c is independently chosen from hydrogen and optionally substituted C₁-C₄ alkyl; or

R^b and R^c, and the nitrogen to which they are attached, form an optionally substituted heterocycloalkyl group; and

where each optionally substituted group is unsubstituted or independently substituted with one or more, such as one, two, or three, substituents independently selected from C₁-C₄ alkyl, aryl, heteroaryl, aryl-C₁-C₄ alkyl-, heteroaryl-C₁-C₄ alkyl-, C₁-C₄ haloalkyl-, -OC₁-C₄ alkyl, -OC₁-C₄ alkylphenyl, -C₁-C₄ alkyl-OH, -OC₁-C₄ haloalkyl, halo, -OH, -NH₂,

-C₁-C₄ alkyl-NH₂, -N(C₁-C₄ alkyl)(C₁-C₄ alkyl), -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)(C₁-C₄ alkylphenyl), -NH(C₁-C₄ alkylphenyl), cyano, nitro, oxo (as a substituent for cycloalkyl, heterocycloalkyl, or heteroaryl), -CO₂H, -C(O)OC₁-C₄ alkyl, -CON(C₁-C₄ alkyl)(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CONH₂, -NHC(O)(C₁-C₄ alkyl), -NHC(O)(phenyl), -N(C₁-C₄ alkyl)C(O)(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)C(O)(phenyl), -C(O)C₁-C₄ alkyl, -C(O)C₁-C₄ alkylphenyl, -C(O)C₁-C₄ haloalkyl, -OC(O)C₁-C₄ alkyl, -SO₂(C₁-C₄ alkyl), -SO₂(phenyl), -SO₂(C₁-C₄ haloalkyl), -SO₂NH₂, -SO₂NH(C₁-C₄ alkyl), -SO₂NH(phenyl), -NHSO₂(C₁-C₄ alkyl), -NHSO₂(phenyl), and -NHSO₂(C₁-C₄ haloalkyl).

[0051] The term “substituted acyl” refers to the groups (substituted alkyl)-C(O)-; (substituted cycloalkyl)-C(O)-; (substituted aryl)-C(O)-; (substituted heteroaryl)-C(O)-; and (substituted heterocycloalkyl)-C(O)-, wherein the group is attached to the parent structure through the carbonyl functionality and wherein substituted alkyl, cycloalkyl, aryl, heteroaryl, and heterocycloalkyl refer respectively to alkyl, cycloalkyl, aryl, heteroaryl, and heterocycloalkyl wherein one or more (such as up to 5, for example, up to 3) hydrogen atoms are replaced by a substituent independently chosen from:

-R^a, -OR^b, -SR^b, guanidine, guanidine wherein one or more of the guanidine hydrogens are replaced with a lower-alkyl group, -NR^bR^c, halo, cyano, nitro, -COR^b, -CO₂R^b, -CONR^bR^c, -OCOR^b, -OCO₂R^a, -OCONR^bR^c, -NR^cCOR^b, -NR^cCO₂R^a, -NR^cCONR^bR^c, -CO₂R^b, -CONR^bR^c, -NR^cCOR^b, -SOR^a, -SO₂R^a, -SO₂NR^bR^c, and -NR^cSO₂R^a,

where R^a is chosen from optionally substituted C₁-C₆ alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^b is chosen from H, optionally substituted C₁-C₆ alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl; and

R^c is independently chosen from hydrogen and optionally substituted C₁-C₄ alkyl; or

R^b and R^c, and the nitrogen to which they are attached, form an optionally substituted heterocycloalkyl group; and

where each optionally substituted group is unsubstituted or independently substituted with one or more, such as one, two, or three, substituents independently selected from C₁-C₄ alkyl, aryl, heteroaryl, aryl-C₁-C₄ alkyl-, heteroaryl-C₁-C₄ alkyl-, C₁-C₄ haloalkyl-, -OC₁-C₄ alkyl, -OC₁-C₄ alkylphenyl, -C₁-C₄ alkyl-OH, -OC₁-C₄ haloalkyl, halo, -OH, -NH₂,

-C₁-C₄ alkyl-NH₂, -N(C₁-C₄ alkyl)(C₁-C₄ alkyl), -NH(C₁-C₄ alkyl),
 -N(C₁-C₄ alkyl)(C₁-C₄ alkylphenyl), -NH(C₁-C₄ alkylphenyl), cyano, nitro, oxo (as a
 substituent for cycloalkyl, heterocycloalkyl, or heteroaryl), -CO₂H, -C(O)OC₁-C₄ alkyl,
 -CON(C₁-C₄ alkyl)(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CONH₂, -NHC(O)(C₁-C₄ alkyl),
 -NHC(O)(phenyl), -N(C₁-C₄ alkyl)C(O)(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)C(O)(phenyl),
 -C(O)C₁-C₄ alkyl, -C(O)C₁-C₄ alkylphenyl, -C(O)C₁-C₄ haloalkyl, -OC(O)C₁-C₄ alkyl, -
 SO₂(C₁-C₄ alkyl), -SO₂(phenyl), -SO₂(C₁-C₄ haloalkyl), -SO₂NH₂, -SO₂NH(C₁-C₄ alkyl),
 -SO₂NH(phenyl), -NHSO₂(C₁-C₄ alkyl), -NHSO₂(phenyl), and -NHSO₂(C₁-C₄ haloalkyl).

[0052] The term “substituted alkoxy” refers to alkoxy wherein the alkyl constituent is substituted (i.e., -O-(substituted alkyl)) wherein “substituted alkyl” refers to alkyl wherein one or more (such as up to 5, for example, up to 3) hydrogen atoms are replaced by a substituent independently chosen from:

-R^a, -OR^b, -SR^b, guanidine, guanidine wherein one or more of the guanidine hydrogens are replaced with a lower-alkyl group, -NR^bR^c, halo, cyano, nitro, -COR^b, -CO₂R^b, -CONR^bR^c, -OCOR^b, -OCO₂R^a, -OCONR^bR^c, -NR^cCOR^b, -NR^cCO₂R^a, -NR^cCONR^bR^c, -CO₂R^b, -CONR^bR^c, -NR^cCOR^b, -SOR^a, -SO₂R^a, -SO₂NR^bR^c, and -NR^cSO₂R^a,

where R^a is chosen from optionally substituted C₁-C₆ alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^b is chosen from H, optionally substituted C₁-C₆ alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl; and

R^c is independently chosen from hydrogen and optionally substituted C₁-C₄ alkyl; or R^b and R^c, and the nitrogen to which they are attached, form an optionally substituted heterocycloalkyl group; and

where each optionally substituted group is unsubstituted or independently substituted with one or more, such as one, two, or three, substituents independently selected from C₁-C₄ alkyl, aryl, heteroaryl, aryl-C₁-C₄ alkyl-, heteroaryl-C₁-C₄ alkyl-, C₁-C₄ haloalkyl-, -OC₁-C₄ alkyl, -OC₁-C₄ alkylphenyl, -C₁-C₄ alkyl-OH, -OC₁-C₄ haloalkyl, halo, -OH, -NH₂, -C₁-C₄ alkyl-NH₂, -N(C₁-C₄ alkyl)(C₁-C₄ alkyl), -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)(C₁-C₄ alkylphenyl), -NH(C₁-C₄ alkylphenyl), cyano, nitro, oxo (as a substituent for cycloalkyl, heterocycloalkyl, or heteroaryl), -CO₂H, -C(O)OC₁-C₄ alkyl, -CON(C₁-C₄ alkyl)(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CONH₂, -NHC(O)(C₁-C₄ alkyl),

-NHC(O)(phenyl), -N(C₁-C₄ alkyl)C(O)(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)C(O)(phenyl), -C(O)C₁-C₄ alkyl, -C(O)C₁-C₄ alkylphenyl, -C(O)C₁-C₄ haloalkyl, -OC(O)C₁-C₄ alkyl, -SO₂(C₁-C₄ alkyl), -SO₂(phenyl), -SO₂(C₁-C₄ haloalkyl), -SO₂NH₂, -SO₂NH(C₁-C₄ alkyl), -SO₂NH(phenyl), -NHSO₂(C₁-C₄ alkyl), -NHSO₂(phenyl), and -NHSO₂(C₁-C₄ haloalkyl). In some embodiments, a substituted alkoxy group is "polyalkoxy" or -O-(optionally substituted alkylene)-(optionally substituted alkoxy), and includes groups such as -OCH₂CH₂OCH₃, and residues of glycol ethers such as polyethyleneglycol, and -O(CH₂CH₂O)_xCH₃, where x is an integer of 2-20, such as 2-10, and for example, 2-5. Another substituted alkoxy group is hydroxyalkoxy or -OCH₂(CH₂)_yOH, where y is an integer of 1-10, such as 1-4.

[0053] The term "substituted alkoxycarbonyl" refers to the group (substituted alkyl)-O-C(O)- wherein the group is attached to the parent structure through the carbonyl functionality and wherein substituted refers to alkyl wherein one or more (such as up to 5, for example, up to 3) hydrogen atoms are replaced by a substituent independently chosen from:

-R^a, -OR^b, -SR^b, guanidine, guanidine wherein one or more of the guanidine hydrogens are replaced with a lower-alkyl group, -NR^bR^c, halo, cyano, nitro, -COR^b, -CO₂R^b, -CONR^bR^c, -OCOR^b, -OCO₂R^a, -OCONR^bR^c, -NR^cCOR^b, -NR^cCO₂R^a, -NR^cCONR^bR^c, -CO₂R^b, -CONR^bR^c, -NR^cCOR^b, -SOR^a, -SO₂R^a, -SO₂NR^bR^c, and -NR^cSO₂R^a,

where R^a is chosen from optionally substituted C₁-C₆ alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^b is chosen from H, optionally substituted C₁-C₆ alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl; and

R^c is independently chosen from hydrogen and optionally substituted C₁-C₄ alkyl; or

R^b and R^c, and the nitrogen to which they are attached, form an optionally substituted heterocycloalkyl group; and

where each optionally substituted group is unsubstituted or independently substituted with one or more, such as one, two, or three, substituents independently selected from C₁-C₄ alkyl, aryl, heteroaryl, aryl-C₁-C₄ alkyl-, heteroaryl-C₁-C₄ alkyl-, C₁-C₄ haloalkyl-, -OC₁-C₄ alkyl, -OC₁-C₄ alkylphenyl, -C₁-C₄ alkyl-OH, -OC₁-C₄ haloalkyl, halo, -OH, -NH₂, -C₁-C₄ alkyl-NH₂, -N(C₁-C₄ alkyl)(C₁-C₄ alkyl), -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)(C₁-C₄ alkylphenyl), -NH(C₁-C₄ alkylphenyl), cyano, nitro, oxo (as a substituent for cycloalkyl, heterocycloalkyl, or heteroaryl), -CO₂H, -C(O)OC₁-C₄ alkyl,

-CON(C₁-C₄ alkyl)(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CONH₂, -NHC(O)(C₁-C₄ alkyl), -NHC(O)(phenyl), -N(C₁-C₄ alkyl)C(O)(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)C(O)(phenyl), -C(O)C₁-C₄ alkyl, -C(O)C₁-C₄ alkylphenyl, -C(O)C₁-C₄ haloalkyl, -OC(O)C₁-C₄ alkyl, -SO₂(C₁-C₄ alkyl), -SO₂(phenyl), -SO₂(C₁-C₄ haloalkyl), -SO₂NH₂, -SO₂NH(C₁-C₄ alkyl), -SO₂NH(phenyl), -NHSO₂(C₁-C₄ alkyl), -NHSO₂(phenyl), and -NHSO₂(C₁-C₄ haloalkyl).

[0054] The term “substituted amino” refers to the group -NHR^d or -NR^dR^e wherein R^d is chosen from: hydroxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted acyl, aminocarbonyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted alkoxy carbonyl, sulfinyl and sulfonyl, and wherein R^e is chosen from: optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycloalkyl, and wherein substituted alkyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl refer respectively to alkyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl wherein one or more (such as up to 5, for example, up to 3) hydrogen atoms are replaced by a substituent independently chosen from:

-R^a, -OR^b, -SR^b, guanidine, guanidine wherein one or more of the guanidine hydrogens are replaced with a lower-alkyl group, -NR^bR^c, halo, cyano, nitro, -COR^b, -CO₂R^b, -CONR^bR^c, -OCOR^b, -OCO₂R^a, -OCONR^bR^c, -NR^cCOR^b, -NR^cCO₂R^a, -NR^cCONR^bR^c, -CO₂R^b, -CONR^bR^c, -NR^cCOR^b, -SOR^a, -SO₂R^a, -SO₂NR^bR^c, and -NR^cSO₂R^a,

where R^a is chosen from optionally substituted C₁-C₆ alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^b is chosen from H, optionally substituted C₁-C₆ alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl; and

R^c is independently chosen from hydrogen and optionally substituted C₁-C₄ alkyl; or

R^b and R^c, and the nitrogen to which they are attached, form an optionally substituted heterocycloalkyl group; and

where each optionally substituted group is unsubstituted or independently substituted with one or more, such as one, two, or three, substituents independently selected from C₁-C₄ alkyl, aryl, heteroaryl, aryl-C₁-C₄ alkyl-, heteroaryl-C₁-C₄ alkyl-, C₁-C₄ haloalkyl-, -OC₁-C₄ alkyl, -OC₁-C₄ alkylphenyl, -C₁-C₄ alkyl-OH, -OC₁-C₄ haloalkyl, halo, -OH, -NH₂, -C₁-C₄ alkyl-NH₂, -N(C₁-C₄ alkyl)(C₁-C₄ alkyl), -NH(C₁-C₄ alkyl),

-N(C₁-C₄ alkyl)(C₁-C₄ alkylphenyl), -NH(C₁-C₄ alkylphenyl), cyano, nitro, oxo (as a substituent for cycloalkyl, heterocycloalkyl, or heteroaryl), -CO₂H, -C(O)OC₁-C₄ alkyl, -CON(C₁-C₄ alkyl)(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CONH₂, -NHC(O)(C₁-C₄ alkyl), -NHC(O)(phenyl), -N(C₁-C₄ alkyl)C(O)(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)C(O)(phenyl), -C(O)C₁-C₄ alkyl, -C(O)C₁-C₄ alkylphenyl, -C(O)C₁-C₄ haloalkyl, -OC(O)C₁-C₄ alkyl, -SO₂(C₁-C₄ alkyl), -SO₂(phenyl), -SO₂(C₁-C₄ haloalkyl), -SO₂NH₂, -SO₂NH(C₁-C₄ alkyl), -SO₂NH(phenyl), -NHSO₂(C₁-C₄ alkyl), -NHSO₂(phenyl), and -NHSO₂(C₁-C₄ haloalkyl); and

wherein optionally substituted acyl, optionally substituted alkoxycarbonyl, sulfinyl and sulfonyl are as defined herein.

[0055] The term “substituted amino” also refers to N-oxides of the groups -NHR^d, and NR^dR^d each as described above. N-oxides can be prepared by treatment of the corresponding amino group with, for example, hydrogen peroxide or m-chloroperoxybenzoic acid. The person skilled in the art is familiar with reaction conditions for carrying out the N-oxidation.

[0056] Compounds of Formula 1 include, but are not limited to, optical isomers of compounds of Formula 1, racemates, and other mixtures thereof. In addition, compounds of Formula I include Z- and E- forms (or *cis*- and *trans*- forms) of compounds with carbon-carbon double bonds. In those situations, the single enantiomers or diastereomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral high-pressure liquid chromatography (HPLC) column. Where compounds of Formula 1 exists in various tautomeric forms, chemical entities of the present invention include all tautomeric forms of the compound.

[0057] Chemical entities of the present invention include, but are not limited to compounds of Formula 1 and all pharmaceutically acceptable forms thereof. Pharmaceutically acceptable forms of the compounds recited herein include pharmaceutically acceptable salts, solvates, crystal forms (including polymorphs and clathrates), chelates, non-covalent complexes, prodrugs, and mixtures thereof. In certain embodiments, the compounds described herein are in the form of pharmaceutically acceptable salts. Hence, the terms “chemical entity” and “chemical entities” also encompass pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures.

[0058] “Pharmaceutically acceptable salts” include, but are not limited to salts with

inorganic acids, such as hydrochlorate, phosphate, diphosphate, hydrobromate, sulfate, sulfinate, nitrate, and like salts; as well as salts with an organic acid, such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, 2-hydroxyethylsulfonate, benzoate, salicylate, stearate, and alkanoate such as acetate, $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$ where n is 0-4, and like salts. Similarly, pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium, and ammonium.

[0059] In addition, if the compound of Formula 1 is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare non-toxic pharmaceutically acceptable addition salts.

[0060] As noted above, prodrugs also fall within the scope of chemical entities, for example ester or amide derivatives of the compounds of Formula 1. The term "prodrugs" includes any compounds that become compounds of Formula 1 when administered to a patient, e.g., upon metabolic processing of the prodrug. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate and like derivatives of functional groups (such as alcohol or amine groups) in the compounds of Formula 1.

[0061] The term "solvate" refers to the chemical entity formed by the interaction of a solvent and a compound. Suitable solvates are pharmaceutically acceptable solvates, such as hydrates, including monohydrates and hemi-hydrates.

[0062] The term "chelate" refers to the chemical entity formed by the coordination of a compound to a metal ion at two (or more) points.

[0063] The term "non-covalent complex" refers to the chemical entity formed by the interaction of a compound and another molecule wherein a covalent bond is not formed between the compound and the molecule. For example, complexation can occur through van der Waals interactions, hydrogen bonding, and electrostatic interactions (also called ionic bonding).

[0064] The term "active agent" is used to indicate a chemical entity which has biological activity. In certain embodiments, an "active agent" is a compound having pharmaceutical utility. For example an active agent may be an anti-cancer therapeutic.

[0065] The term "therapeutically effective amount" of a chemical entity of this invention means an amount effective, when administered to a human or non-human patient, to treat a disease, e.g., a therapeutically effective amount may be an amount sufficient to treat a disease or disorder responsive to kinase inhibition. The therapeutically effective amount may be ascertained experimentally, for example by assaying blood concentration of the chemical entity, or theoretically, by calculating bioavailability.

[0066] By "significant" is meant any detectable change that is statistically significant in a standard parametric test of statistical significance such as Student's T-test, where $p < 0.05$.

[0067] "Patient" refers to an animal, such as a mammal, for example a human, that has been or will be the object of treatment, observation or experiment. The methods of the invention can be useful in both human therapy and veterinary applications. In some embodiments, the patient is a mammal, and in some embodiments the patient is human.

[0068] By "angiogenic kinase" is meant a kinase involved in angiogenesis and includes but is not limited to a kinase chosen from EphB₄, VEGFR2 and PDGFR β .

[0069] By "oncogenic kinase" is meant a kinase having a direct role in a cell signaling pathway that leads to cellular transformation. When overexpressed or aberrantly expressed, such kinases may have oncogenic activity. Oncogenic kinases include but are not limited to c-Kit.

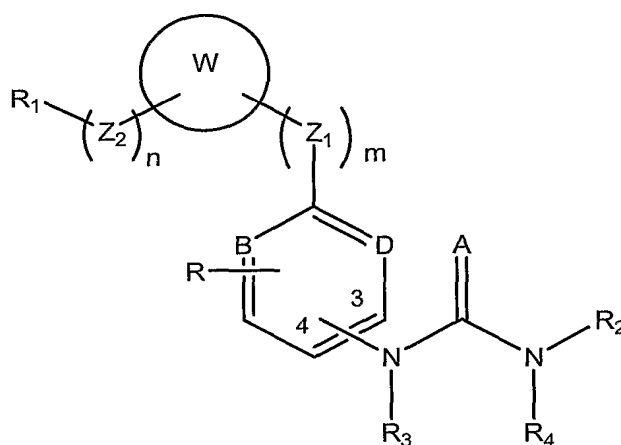
[0070] "Treatment" or "treating" means any treatment of a disease in a patient, including:

- a) preventing the disease, that is, causing the clinical symptoms of the disease not to develop;
- b) inhibiting the disease;
- c) slowing or arresting the development of clinical symptoms; and/or
- d) relieving the disease, that is, causing the regression of clinical symptoms.

[0071] "Diseases or disorders responsive to kinase modulation" refer to pathologic conditions that depend, at least in part, on the activity of one or more protein kinases, for example, angiogenic kinases and/or oncogenic kinases. Kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities including cell proliferation, differentiation, and invasion. Diseases responsive to kinase modulation include but are not limited to tumor growth, angiogenesis supporting solid tumor growth, and diseases characterized by excessive local vascularization such as diabetic retinopathy, macular degeneration, and inflammation.

[0072] “Change in angiogenesis” refers to a change in the vascular network or quality of vasculature. Change in angiogenesis may be measured by many parameters and, for instance, may be assessed by delayed appearance of neovascular structures, slowed development of neovascular structures, decreased occurrence of neovascular structures, changes in vascular permeability, changes in blood flow, slowed or decreased severity of angiogenesis-dependent disease effects, arrested angiogenic growth, or regression of previous angiogenic growth.

[0073] Provided herein is at least one chemical entity chosen from compounds of Formula 1



(Formula 1)

and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, wherein

A is chosen from O and S;

B and D are chosen from CH and N, provided that at least one of B and D is CH;

R represents 0 to 2 substituents independently chosen from hydroxy, nitro, cyano, optionally substituted amino, aminocarbonyl, halo, carboxy, optionally substituted acyl, optionally substituted alkoxy, optionally substituted alkoxy, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, sulfanyl, sulfinyl, sulfonyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycloalkyl;

R₁ is optionally substituted heteroaryl;

W is optionally substituted heteroaryl;

Z₁ is -CR₅R₆- wherein each R₅ and R₆ is independently chosen from hydrogen, optionally substituted C₁-C₆ alkyl, and halo;

m is chosen from 0, 1, and 2;

Z_2 is $-\text{CR}_7\text{R}_8-$ wherein each R_7 and R_8 is independently chosen from hydrogen, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, and halo;

n is chosen from 0, 1, and 2;

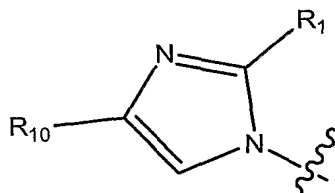
R_2 is optionally substituted aryl; and

R_3 and R_4 are each independently chosen from hydrogen, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, optionally substituted aryl, and optionally substituted heteroaryl,

provided that

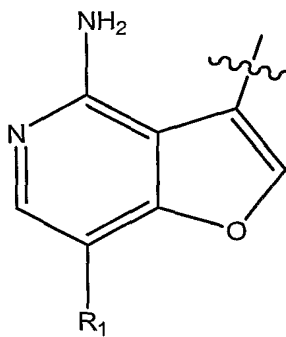
R_1 is not 4-aminothieno[2,3-d]pyrimidine-6-yl when n is 0, m is 0, W is 1-methyl-1H-imidazol-4,5-diyl, A is CH, R is absent, R_3 and R_4 are hydrogen, and R_2 is chosen from phenyl and 2-fluoro-5-(trifluoromethyl)phenyl;

when n is 0, m is 0, A is CH, and R is absent, W is not



where R_{10} is chosen from CF_3 , halo; CN, $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_1\text{-C}_6$ alkenyl; $\text{C}_3\text{-C}_8$ cycloalkyl optionally substituted with a group chosen from hydroxy, cyano, and methoxy, $\text{C}_1\text{-C}_8$ alkoxy; $\text{C}_1\text{-C}_4$ alkyloxyalkyl; $\text{C}_1\text{-C}_8$ alkylthio; $\text{C}_1\text{-C}_4$ alkylthioalkyl; $\text{C}_1\text{-C}_8$ dialkylamino; $\text{C}_1\text{-C}_4$ dialkylaminoalkyl; alkoxycarbonyl optionally substituted with a group chosen from carbocyclyl and heterocyclyl; aryl and heterocyclyl, wherein the aryl and heterocyclyl groups may be optionally substituted with a group chosen from halo, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ alkenyl, CN, dimethylamino, methoxycarbonyl, methoxy, aryl, and heterocyclyl;

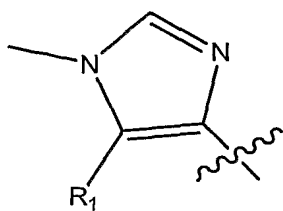
when n is 0, m is 0, A is CH, R is absent, and R_2 is 2-fluoro-5-trifluoromethylphenyl,



W is not

where R_1 is pyridin-3-yl; and

when n is 0, m is 0, A is CH, R is absent, and R_2 is chosen from phenyl and 2-fluoro-5-(trifluoromethyl)phenyl, W is not



where R₁ is 4-aminoethieno[2,3-d]pyrimidin-6-yl.

[0074] In some embodiments, R represents 1 or 2 substituents independently chosen from halo, C₁-C₂ alkyl, and C₁-C₂ alkoxy. In some embodiments, R represents 1 or 2 substituents independently chosen from halo, methyl, and methoxy. In some embodiments, R represents a substituent chosen from halo, methyl, and methoxy.

[0075] In some embodiments, R₁ is chosen from pyridinyl, and substituted pyridinyl chosen from mono-, di-, and tri-substituted pyridinyls wherein the substituents on the substituted pyridinyl are independently chosen from hydroxy, nitro, cyano, optionally substituted amino, aminocarbonyl, halo, carboxy, optionally substituted acyl, optionally substituted alkoxycarbonyl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, sulfanyl, sulfinyl, sulfonyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycloalkyl.

[0076] In some embodiments, R₁ is chosen from pyridin-4-yl, and substituted pyridin-4-yl chosen from mono-, di-, and tri-substituted pyridin-4-yls and wherein substituents on the substituted pyridin-4-yl are independently chosen from hydroxy, nitro, cyano, optionally substituted amino, aminocarbonyl, halo, carboxy, optionally substituted acyl, optionally substituted alkoxycarbonyl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, sulfanyl, sulfinyl, sulfonyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycloalkyl.

[0077] In some embodiments, the substituents on the substituted pyridin-4-yl are independently chosen from hydroxy, nitro, cyano, optionally substituted amino, halo, carboxy, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, C₁-C₆ alkylsulfanyl, C₁-C₆ acyl, C₁-C₆ alkoxycarbonyl, optionally substituted heteroaryl, and heterocycloalkyl.

[0078] In some embodiments, the substituents on the substituted pyridin-4-yl are independently chosen from hydroxy, cyano, halo, optionally substituted C₁-C₂ alkyl, and

optionally substituted C₁-C₂ alkoxy.

[0079] In some embodiments, R₁ is pyridin-4-yl.

[0080] In some embodiments, W is chosen from 5- and 6-membered heteroaryl wherein the heteroaryl ring contains at least one nitrogen and optionally includes one, two, or three additional heteroatoms, selected from N, O, and S in the ring.

[0081] In some embodiments, W is chosen from pyridyl, pyrazinyl, pyrimidinyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, tetrazolyl, thienyl, furanyl, pyridizynyl, triazolyl, and pyrrolyl.

[0082] In some embodiments, W is 1H-imidazol-1,2-diyl.

[0083] In some embodiments, m is 1 and at least one of R₅ and R₆ is hydrogen. In some embodiments, R₅ and R₆ are hydrogen.

[0084] In some embodiments, m is 0.

[0085] In some embodiments, n is 1 and at least one of R₇ and R₈ is hydrogen. In some embodiments, R₇ and R₈ are hydrogen.

[0086] In some embodiments, n is 0.

[0087] In some embodiments, R₂ is chosen from phenyl, and

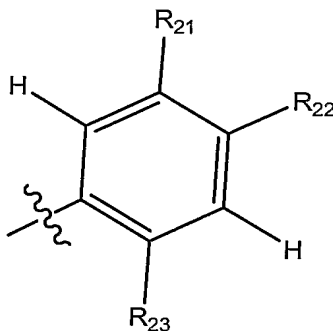
substituted phenyl chosen from mono-, di-, and tri-substituted phenyls wherein the substituents on the substituted phenyl are independently chosen from hydroxy, nitro, cyano, optionally substituted amino, aminocarbonyl, halo, carboxy, optionally substituted acyl, optionally substituted alkoxycarbonyl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted aryloxy, sulfanyl, sulfinyl, sulfonyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycloalkyl.

[0088] In some embodiments, the substituents on the substituted phenyl are independently chosen from hydroxy, nitro, cyano, optionally substituted amino, halo, carboxy, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted phenoxy, C₁-C₆ alkylsulfanyl, C₁-C₆ acyl, C₁-C₆ alkoxycarbonyl, optionally substituted heteroaryl, and heterocycloalkyl.

[0089] In some embodiments, the substituents on the substituted phenyl are independently chosen from hydroxy, cyano, halo, optionally substituted C₁-C₂ alkyl, phenoxy, and optionally substituted C₁-C₂ alkoxy.

[0090] In some embodiments, the substituents on the substituted phenyl are independently chosen from halo, methyl, methoxy, ethoxy, and trifluoromethyl.

[0091] In some embodiments, R_2 is



wherein

R_{21} is chosen from hydrogen, halo and optionally substituted lower alkyl;

R_{22} is chosen from hydrogen, halo, lower alkoxy, and lower alkyl; and

R_{23} is chosen from hydrogen, lower alkyl, optionally substituted phenoxy, lower alkoxy, and halo.

[0092] In some embodiments, R_{21} is chosen from hydrogen, halo, methyl, and trifluoromethyl.

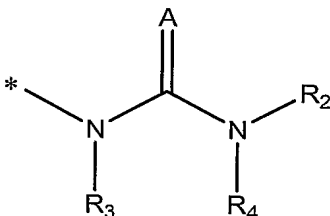
[0093] In some embodiments, R_{22} is chosen from hydrogen, halo, methoxy, and methyl.

[0094] In some embodiments, R_{23} is chosen from hydrogen, methyl, methoxy, ethoxy, and halo.

[0095] In some embodiments, R_3 and R_4 are each independently chosen from hydrogen and methyl.

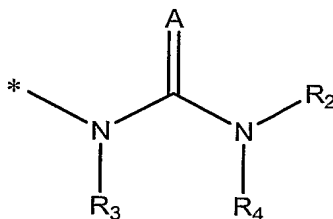
[0096] In some embodiments, R_3 and R_4 are hydrogen.

[0097] In some embodiments, the group having the structure:



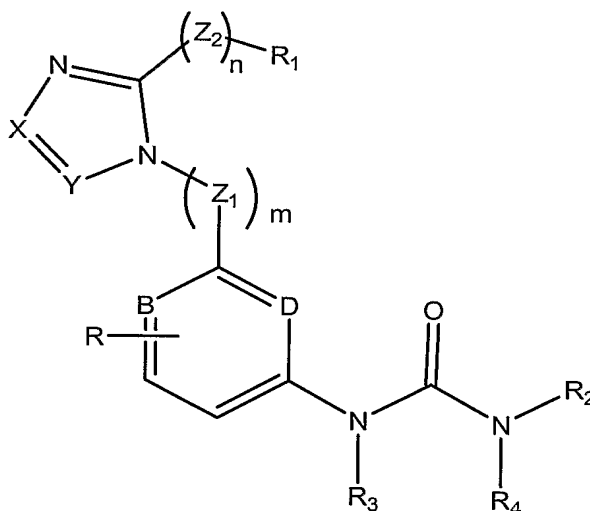
is bonded to the 3-position of the ring. In some embodiments, that group is bonded to the 3-position of the ring and A is O.

[0098] In some embodiments, the group having the structure:



is bonded to the 4-position of the ring. In some embodiments, that group is bonded to the 4-position of the ring and A is O.

[0099] Provided herein is at least one chemical entity chosen from compounds of Formula 2



(Formula 2)

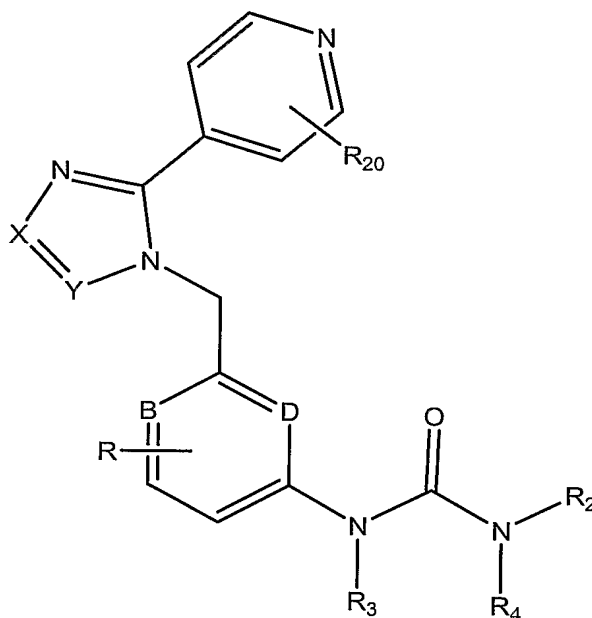
and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, wherein R_1 , Z_2 , n , Z_1 , m , B , D , R , R_2 , R_3 , and R_4 are as described for compounds of Formula 1 and wherein

X and Y are independently chosen from CH and N.

[00100] In some embodiments, X and Y are CH.

[00101] In some embodiments, X and Y are N.

[00102] Provided herein is at least one chemical entity chosen from compounds of Formula 3



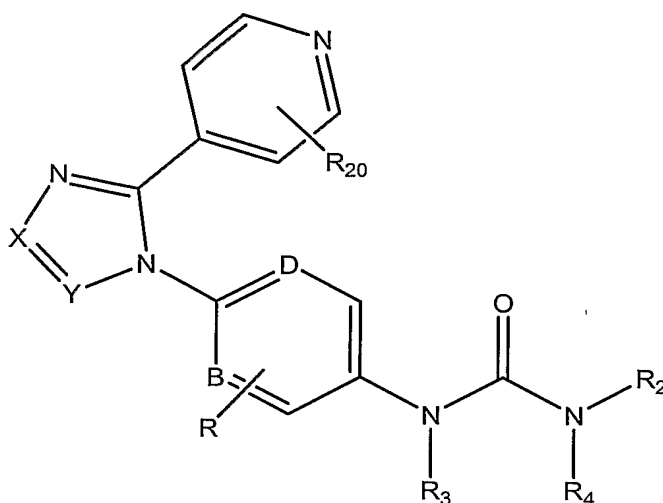
(Formula 3)

and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, wherein B, D, R, R₂, R₃, and R₄ are as described for compounds of Formula 1, wherein X and Y are as described for compounds of Formula 2, and wherein

R₂₀ represents 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, optionally substituted amino, aminocarbonyl, halo, carboxy, optionally substituted acyl, optionally substituted alkoxycarbonyl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, sulfanyl, sulfinyl, sulfonyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycloalkyl.

[00103] In some embodiments, R₂₀ is optionally substituted amino. In some embodiments, R₂₀ is amino.

[00104] Provided herein is at least one chemical entity chosen from compounds of Formula 4



(Formula 4)

and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof wherein B, D, R, R₂, R₃, and R₄ are as described for compounds of Formula 1, wherein X and Y are as described for compounds of Formula 2, and wherein R₂₀ is as described for compounds of Formula 3.

[00105] In certain embodiments, the compound of Formula 1 is chosen from
 1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
 1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
 1-(4-Methoxy-3-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-
 urea;
 1-(2,4-Dimethoxy-5-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-
 phenyl]-urea;
 1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-
 urea;
 1-(4-Methyl-3-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-
 urea;
 1-(5-Bromo-2,4-dimethoxy-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
 1-(5-Chloro-2-methoxy-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
 1-(2-Fluoro-5-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-
 urea;
 1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-
 thiourea;

1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[3-(5-pyridin-4-yl-tetrazol-1-ylmethyl)-phenyl]-urea;
1-(5-Chloro-2-methoxy-phenyl)-3-[2-methyl-3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[2-methyl-3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(5-Bromo-2-methoxy-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(2-Ethoxy-5-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(5-Bromo-2-ethoxy-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(5-Chloro-2-phenoxy-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(5-Bromo-2-methyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[4-methyl-3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(5-Chloro-2-methyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(2-Chloro-5-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[3-(1-pyridin-4-yl-1H-imidazole-2-carbonyl)-phenyl]-urea;
1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[2-methyl-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[3-(4-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(2-Methyl-5-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(2-Methoxy-5-methyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-[5-Bromo-2-(2-dimethylamino-ethoxy)-phenyl]-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(5-Bromo-2-fluoro-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(4-Fluoro-3-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
1-(5-Chloro-2-methoxy-phenyl)-3-[2-methyl-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(2-Fluoro-5-trifluoromethyl-phenyl)-3-[2-methyl-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;

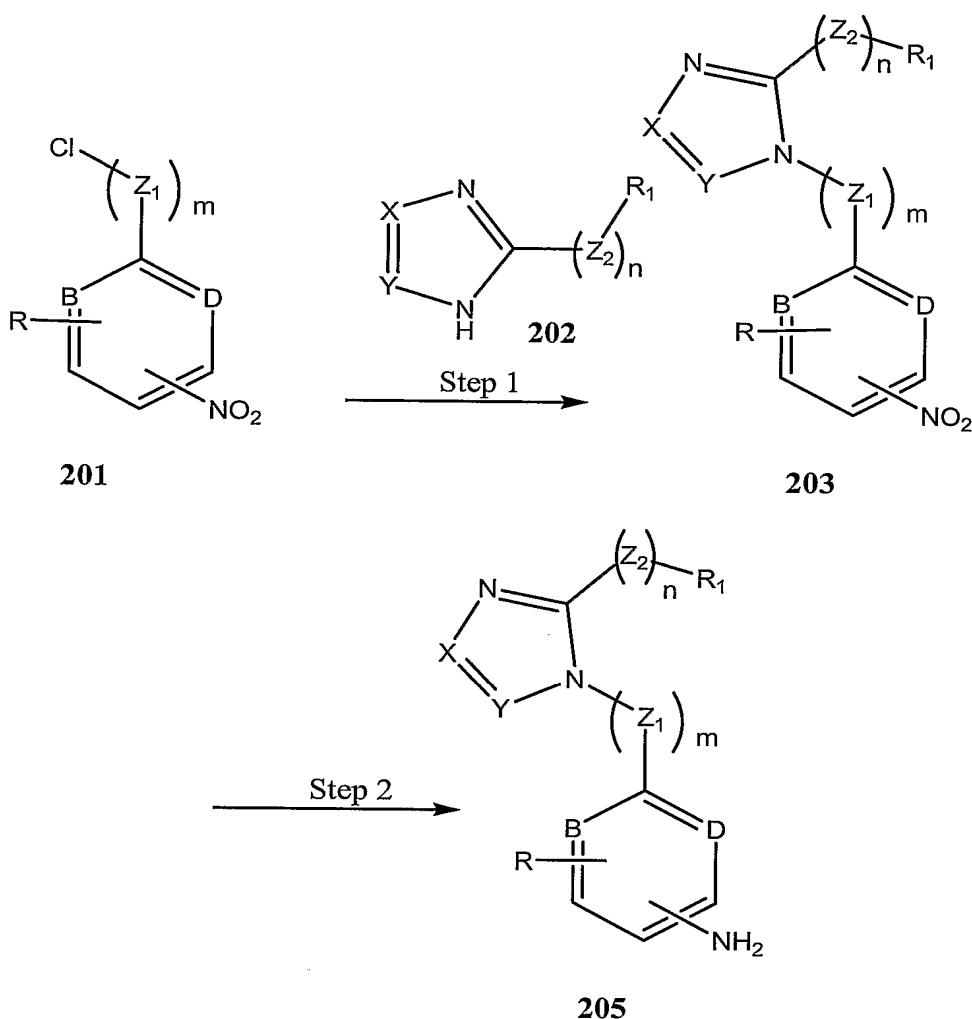
- 1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[2-methyl-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(2,4-Dimethoxy-5-trifluoromethyl-phenyl)-3-[2-methyl-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-{3-[1-(2-pyridin-4-yl-imidazol-1-yl)-ethyl]-phenyl}-urea;
- 1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 4-(1-{3-[3-(2-Methoxy-5-trifluoromethyl-phenyl)-ureido]-benzyl}-1H-imidazol-2-yl)-pyridine-2-carboxylic acid methylamide;
- 1-(5-Bromo-2-methoxy-phenyl)-3-[2-methyl-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(5-Chloro-2-fluoro-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(2-Fluoro-5-methyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(2-Fluoro-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(2,4-Dimethoxy-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-[2-Chloro-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea;
- 1-(4-Methyl-3-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(5-Chloro-2-methoxy-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(2-Chloro-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(2-Methoxy-5-methyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(2,4-Dimethyl-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(5-Bromo-2-methoxy-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(5-Bromo-2,4-dimethoxy-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(5-Bromo-2-methoxy-phenyl)-3-[2-methoxy-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(5-Bromo-2,4-dimethoxy-phenyl)-3-[2-methoxy-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-[2-Fluoro-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea;
- 1-(5-Chloro-2-methoxy-phenyl)-3-[2-fluoro-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;

- 1-(4-Chloro-2-methoxy-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(5-Bromo-2-methoxy-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(2-Methoxy-4-methyl-5-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(2-Fluoro-5-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(2-Ethoxy-5-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(4-Chloro-2-methoxy-5-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(4-Chloro-3-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-3-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(4-Methoxy-3-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(4-Chloro-3-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(4-Fluoro-3-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-[2-Methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-3-(4-methyl-3-trifluoromethyl-phenyl)-urea;
- 1-(5-Bromo-2-ethoxy-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(5-Chloro-2-methoxy-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[6-(2-pyridin-4-yl-imidazol-1-yl)-pyridin-3-yl]-urea;
- 1-(2-Fluoro-5-trifluoromethyl-phenyl)-3-[6-(2-pyridin-4-yl-imidazol-1-yl)-pyridin-3-yl]-urea;
- 1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-2-trifluoromethyl-phenyl]-urea;
- 1-[2-Fluoro-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-3-(2-fluoro-5-trifluoromethyl-phenyl)-urea;

1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-ylmethyl-imidazol-1-yl)-phenyl]-urea;
1-(2-Fluoro-5-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-ylmethyl-imidazol-1-yl)-phenyl]-urea;
1-[2-Methyl-4-(2-pyridin-4-ylmethyl-imidazol-1-yl)-phenyl]-3-(4-methyl-3-trifluoromethyl-phenyl)-urea;
1-(2-Nitro-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
1-(2-Amino-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
1-[2-Cyano-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea;
4-(1-{4-[3-(2-Methoxy-5-trifluoromethyl-phenyl)-ureido]-3-methyl-phenyl}-1H-imidazol-2-yl)-pyridine-2-carboxylic acid methylamide;
1-[2-Aminomethyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea;
2-[3-(2-Fluoro-5-trifluoromethyl-phenyl)-ureido]-N-methyl-5-(2-pyridin-4-yl-imidazol-1-yl)-benzamide;
1-{5-[2-(2-Amino-pyridin-4-yl)-imidazol-1-yl]-2-methyl-phenyl}-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea;
1-{3-[2-(2-Amino-pyridin-4-yl)-imidazol-1-ylmethyl]-phenyl}-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea;
1-[2-Methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-3-(3-methylsulfanyl-phenyl)-urea; and
1-(3-Methylsulfanyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof.

[00106] Methods for obtaining the novel compounds described herein will be apparent to those of ordinary skill in the art, suitable procedures being described, for example, in the reaction scheme and example below, and in the references cited herein.

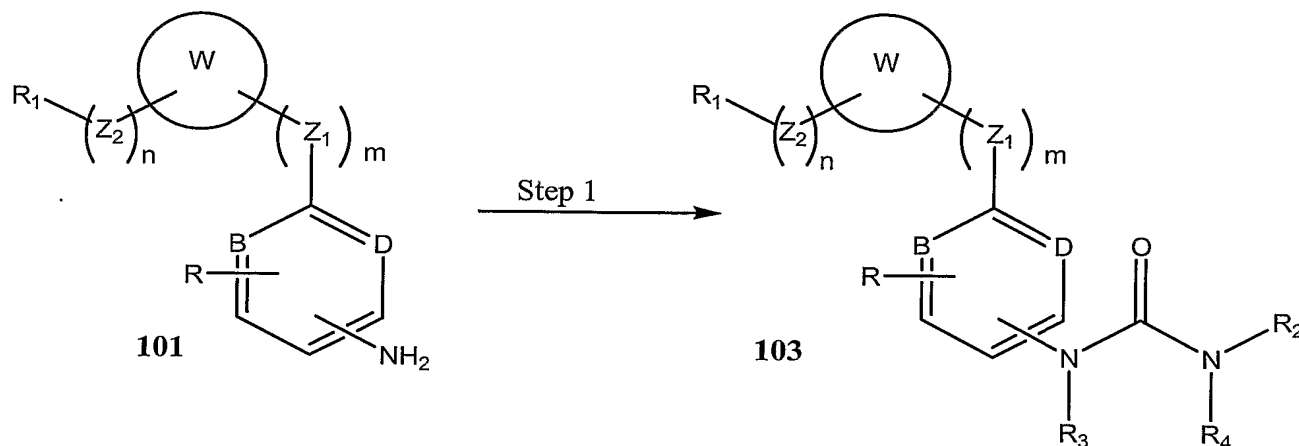
Reaction Scheme 1



[00107] Referring to Reaction Scheme 1, Step 1, an inert solvent such as DMF is added to a compound of Formula 202, a base such as sodium carbonate, and an excess (such as about 1.5 equivalents) of a compound of Formula 201. The mixture is warmed to about 50 °C for about 4h. The product, a compound of Formula 203, is isolated and optionally purified.

[00108] Referring to Reaction Scheme 1, Step 2, a polar, protic solvent such as ethanol is added to a compound of Formula 203 and 10% palladium on charcoal or other hydrogenation catalyst under an atmosphere of argon. The atmosphere is purged with H_2 on a Parr shaker type hydrogenation apparatus, and the mixture is shaken for about 4 h at about 50 psi H_2 . The product, a compound of Formula 205, is isolated and optionally purified.

Reaction Scheme 2



[00109] Referring to Reaction Scheme 2, Step 1, a compound of Formula 101 is dissolved in an inert solvent (such as dichloromethane, DMF, or a mixture thereof) to which about an equivalent of a compound of formula $R_2\text{-NCO}$ is added. The product, a compound of Formula 103, is isolated and optionally purified.

[00110] In some embodiments, the chemical entities described herein are administered as a pharmaceutical composition or formulation. Accordingly, the invention provides pharmaceutical formulations comprising at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, together with at least one pharmaceutically acceptable vehicle chosen from carriers, adjuvants, and excipients.

[00111] Pharmaceutically acceptable vehicles must be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the patient being treated. The vehicle can be inert or it can possess pharmaceutical benefits. The amount of vehicle employed in conjunction with the chemical entity is sufficient to provide a practical quantity of material for administration per unit dose of the chemical entity.

[00112] Exemplary pharmaceutically acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; synthetic oils; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, and corn oil; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; phosphate buffer solutions; emulsifiers, such as the TWEENS; wetting agents, such sodium lauryl sulfate;

coloring agents; flavoring agents; tableting agents; stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

[00113] Optional active agents may be included in a pharmaceutical composition, which do not substantially interfere with the activity of the chemical entity of the present invention.

[00114] A therapeutically effective amount of at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, is mixed with a suitable pharmaceutical acceptable vehicle. In instances in which the chemical entity exhibits insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as TWEEN, or dissolution in aqueous sodium bicarbonate.

[00115] Upon mixing or addition of the chemical entity described herein, the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the chemical entity in the chosen vehicle. The therapeutically effective amount may be empirically determined.

[00116] Chemical entities described herein may be administered orally, topically, parenterally, intravenously, by intramuscular injection, by inhalation or spray, sublingually, transdermally, via buccal administration, rectally, as an ophthalmic solution, or by other means, in dosage unit formulations.

[00117] Dosage formulations suitable for oral use, include, for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents, such as sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide pharmaceutically elegant and palatable preparations. In some embodiments, oral formulations contain from 0.1 to 99% of at least one chemical entity described herein. In some embodiments, oral formulations contain at least 5% (weight %) of at least one chemical entity described herein. Some embodiments contain from 25% to 50% or from 5% to 75 % of at least one chemical entity described herein.

[00118] Orally administered compositions also include liquid solutions, emulsions,

suspensions, powders, granules, elixirs, tinctures, syrups, and the like. The pharmaceutically acceptable carriers suitable for preparation of such compositions are well known in the art. Oral formulations may contain preservatives, flavoring agents, sweetening agents, such as sucrose or saccharin, taste-masking agents, and coloring agents.

[00119] Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent.

[00120] Chemical entities described herein can be incorporated into oral liquid preparations such as aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, for example. Moreover, formulations comprising these chemical entities can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations can contain conventional additives, such as suspending agents (e.g., sorbitol syrup, methyl cellulose, glucose/sugar, syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminum stearate gel, and hydrogenated edible fats), emulsifying agents (e.g., lecithin, sorbitan monoleate, or acacia), non-aqueous vehicles, which can include edible oils (e.g., almond oil, fractionated coconut oil, silyl esters, propylene glycol and ethyl alcohol), and preservatives (e.g., methyl or propyl p-hydroxybenzoate and sorbic acid).

[00121] For a suspension, typical suspending agents include methylcellulose, sodium carboxymethyl cellulose, AVICEL RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate.

[00122] Aqueous suspensions contain the active material(s) in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are chosen from suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents; naturally-occurring phosphatides, for example, lecithin, and condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, and condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, and condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol substitute, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan substitute. The aqueous suspensions may also contain one or more preservatives, for

example ethyl, or n- propyl p-hydroxybenzoate.

[00123] Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example peanut oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[00124] Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or peanut oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate.

[00125] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above.

[00126] Tablets typically comprise conventional pharmaceutically acceptable adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmellose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, can be useful adjuvants for chewable tablets. Capsules (including time release and sustained release formulations) typically comprise one or more solid diluents disclosed above. The selection of carrier components often depends on secondary considerations like taste, cost, and shelf stability.

[00127] Such compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that the chemical entity is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to

extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methylcellulose phthalate, ethyl cellulose, Eudragit coatings, waxes and shellac.

[00128] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

[00129] Pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable vehicle, for example as a solution in 1,3-butanediol. Among the acceptable vehicles that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be useful in the preparation of injectables.

[00130] Chemical entities described herein may be administered parenterally in a sterile medium. Parenteral administration includes subcutaneous injections, intravenous, intramuscular, intrathecal injection or infusion techniques. Chemical entities described herein, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle. In many compositions for parenteral administration the carrier comprises at least 90% by weight of the total composition. In some embodiments, the carrier for parenteral administration is chosen from propylene glycol, ethyl oleate, pyrrolidone, ethanol, and sesame oil.

[00131] Chemical entities described herein may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

[00132] Chemical entities described herein may be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the

eye, in the form of gels, creams, and lotions and for application to the eye. Topical compositions may be in any form including, for example, solutions, creams, ointments, gels, lotions, milks, cleansers, moisturizers, sprays, skin patches, and the like.

[00133] Such solutions may be formulated as 0.01% -10% isotonic solutions, pH from 2 to 12, such as from 5 to 7, with appropriate salts. Chemical entities described herein may also be formulated for transdermal administration as a transdermal patch.

[00134] Topical compositions comprising at least one chemical entity described herein can be admixed with a variety of carrier materials well known in the art, such as, for example, water, alcohols, aloe vera gel, allantoin, glycerine, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate, and the like.

[00135] Other materials suitable for use in topical carriers include, for example, emollients, solvents, humectants, thickeners and powders. Examples of each of these types of materials, which can be used singly or as mixtures of one or more materials, are as follows:

[00136] Representative emollients include stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, iso-propyl isostearate, stearic acid, iso-butyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, dimethylpolysiloxane, di-n-butyl sebacate, iso-propyl myristate, iso-propyl palmitate, iso-propyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, and myristyl myristate; propellants, such as propane, butane, iso-butane, dimethyl ether, carbon dioxide, and nitrous oxide; solvents, such as ethyl alcohol, methylene chloride, iso-propanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethyl sulphoxide, dimethyl formamide, tetrahydrofuran; humectants, such as glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, and gelatin; and powders, such as chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, trialkyl aryl ammonium smectites, chemically modified magnesium aluminium silicate, organically modified montmorillonite clay, hydrated aluminium silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, and ethylene glycol monostearate.

[00137] Chemical entities described herein may also be topically administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar

vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

[00138] Other compositions useful for attaining systemic delivery of the chemical entity include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol, and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose, and hydroxypropyl methylcellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

[00139] Compositions for inhalation typically can be provided in the form of a solution, suspension or emulsion that can be administered as a dry powder or in the form of an aerosol using a conventional propellant (e.g., dichlorodifluoromethane or trichlorofluoromethane).

[00140] The compositions of the present invention may also optionally comprise an activity enhancer. The activity enhancer can be chosen from a wide variety of molecules that function in different ways to enhance or be independent of therapeutic effects of the chemical entities described herein. Particular classes of activity enhancers include skin penetration enhancers and absorption enhancers.

[00141] Pharmaceutical compositions of the invention may also contain additional active agents that can be chosen from a wide variety of molecules, which can function in different ways to enhance the therapeutic effects of at least one chemical entity described herein. These optional other active agents, when present, are typically employed in the compositions of the invention at a level ranging from 0.01% to 15%. Some embodiments contain from 0.1% to 10% by weight of the composition. Other embodiments contain from 0.5% to 5% by weight of the composition.

[00142] The invention can include packaged pharmaceutical formulations. Such packaged formulations include a pharmaceutical composition comprising at least one chemical entity chosen from compounds of Formula 1 and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, in a container and instructions for using the composition to treat a mammal (typically a human patient). In some embodiments, the instructions are for using the pharmaceutical composition to treat a patient suffering from a disease responsive to kinase inhibition. The invention includes providing prescribing information; for example, to a patient or health care provider, or as a label in a packaged pharmaceutical formulation. Prescribing information may include for example efficacy, dosage and administration, contraindication and adverse reaction

information pertaining to the pharmaceutical formulation.

[00143] In all of the foregoing the chemical entities can be administered alone, as mixtures, or in combination with other active agents.

[00144] The compounds of the present invention can be useful for the treatment of diseases and disorders responsive to kinase modulation.

[00145] In certain embodiments, compounds described herein are modulators of protein kinases. In certain embodiments, the compounds described herein are inhibitors of the protein kinases. In certain embodiments, the compounds inhibit at least one kinase chosen from EphB₄, Tie2, c-Kit, and VEGFR2 kinases. In certain embodiments, the compounds inhibit more than one kinase chosen from EphB₄, Tie2, c-Kit, and VEGFR2 kinases.

[00146] Accordingly, the invention includes a method of treating a patient, such as a human patient, having a disease or disorder responsive to kinase modulation, comprising administering to the patient a therapeutically effective amount of at least one chemical entity described herein.

[00147] A method of treating a patient having a disease or disorder responsive to kinase modulation, particularly VEGFR2 modulation, comprising administering to the patient a therapeutically effective amount of one or more of the compounds of Formula I is provided.

[00148] Also provided is the use of at least one chemical entity described herein for the manufacture of a medicament for the treatment of a patient having a disease or disorder responsive to kinase modulation, particularly VEGFR2 modulation. Also provided is the use of at least one chemical entity described herein for the manufacture of a medicament for the treatment of a patient having angiogenesis.

[00149] In some embodiments, the compounds of Formula I inhibit at least one kinase chosen from EphB₄, Tie2, c-Kit, and VEGFR2 and can be useful for the treatment of diseases and disorders responsive to modulation of at least one of such kinases. In some embodiments, the disease or disorder is characterized by angiogenesis supporting solid tumor growth or dysregulated local vascularization.

[00150] Methods of treatment also include modulating kinase activity, by inhibiting ATP binding or hydrolysis by a kinase or by some other mechanism, *in vivo*, in a patient suffering from a disease or disorder responsive to kinase modulation, by administering a therapeutically effective amount of at least one chemical entity described herein to inhibit kinase activity *in vitro*.

[00151] In some embodiments, the condition responsive to kinase modulation is cancer

or a disease or disorder characterized by a change in angiogenesis.

[00152] The invention includes a method of treating a patient having cancer or a disease or disorder characterized by a change in angiogenesis by administering at least one chemical entity described herein. The invention provides methods of treatment in which the chemical entity is the only active agent given to a patient and also includes methods of treatment in which at least one chemical entity described herein is given to a patient in combination with one or more additional active agents.

[00153] Certain compounds described herein can be useful for treating a patient suffering from a disease or disorder responsive to kinase modulation.

[00154] In certain embodiments, the conditions, diseases and/or disorders that are affected using at least one chemical entity described herein and compositions comprising such chemical entities include, but are not limited to, psoriasis, angiogenesis, cancer (for example, chronic myelogenous leukemia, gastrointestinal stromal tumors, non-small cell lung cancer, breast cancer, ovarian cancer, recurrent ovarian cancer, prostate cancer such as hormonal refractory prostate cancer, kidney cancer, head and neck cancer, or colorectal cancer), immunoregulation (graft rejection), atherosclerosis, rheumatoid arthritis, Parkinson's disease, Alzheimer's disease, diabetes (for example insulin resistance or diabetic retinopathy), septic shock, and the like.

[00155] In certain embodiments, the conditions, diseases and/or disorders that are affected using at least one chemical entity described herein and compositions comprising such chemical entities are female reproductive female reproductive disorders and conditions. In certain embodiments, the female reproductive disorders and conditions are chosen from endometriosis, endometrial carcinoma, gynecologic bleeding disorders, irregular menstrual cycles, ovulation, premenstrual syndrome (PMS), and menopausal dysfunction.

[00156] Because kinases play an active role in angiogenesis certain compounds described herein can be useful for modulating angiogenesis. Angiogenesis, the formation of new blood vessels from preexisting ones, plays a critical role in many pathological settings, including cancer, chronic inflammation, diabetic retinopathy and macular degeneration. Angiogenesis is regulated by multiple cell-signaling pathways, including pathways controlled by cellular kinases. Blocking angiogenesis, through the modulation of cell kinases, therefore, can represent effective approach to the treatment of diseases such as cancer. Thus methods of treatment include administering a therapeutically effective amount of at least one chemical entity described herein to treat these diseases or disorders, e.g., to decrease the symptoms or slow the progression of these diseases or disorders by inhibiting the rate of angiogenesis in a

tissue.

[00157] The invention further includes methods for combination drug therapy, in which at least one chemical entity described herein is given to a patient together with one or more other active agents. Thus in one embodiment the invention provides a method of treating cancer, which comprises administering to a patient in need thereof an effective amount of at least one chemical entity described herein together with a second active agent, which can be useful for treating cancer. For example the second agent may be an antitumor agent. Treatment with the second active agent may be prior to, concomitant with, or following treatment with at least one chemical entity described herein.

[00158] In certain embodiments, at least one chemical entity chosen from compounds of Formula 1, and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, is combined with at least one second active agent in a single dosage form. Radiotherapeutic anti-tumor agents may also be used alone or in combination with chemotherapeutic agents. Suitable anti-tumor therapeutics that may be used in combination with at least one chemical entity described herein. Examples of anti-tumor therapeutics include, in general, microtubule-stabilizing agents (such as paclitaxel (also known as Taxol), docetaxel (also known as Taxotere), epothilone A, epothilone B, desoxyepothilone A, desoxyepothilone B or their derivatives); microtubule-disruptor agents; alkylating agents, anti-metabolites; epidophyllotoxin; an antineoplastic enzyme; a topoisomerase inhibitor; procarbazine; mitoxantrone; platinum coordination complexes; biological response modifiers and growth inhibitors; hormonal/anti-hormonal therapeutic agents and haematopoietic growth factors.

[00159] Example classes of anti-tumor therapeutics include, for example, the anthracycline family of drugs, the vinca drugs, the mitomycins, the bleomycins, the cytotoxic nucleosides, the taxanes, the epothilones, discodermolide, the pteridine family of drugs, diynenes and the podophyllotoxins. Particularly useful members of those classes include, for example, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, dichloro-methotrexate, mitomycin C, porfiromycin, herceptin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin or podo-phyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide, melphalan, vinblastine, vincristine, leurosine, vindesine, leurosine, paclitaxel and the like. Other useful antineoplastic agents include estramustine, cisplatin, carboplatin, cyclophosphamide, bleomycin, tamoxifen, ifosamide, melphalan, hexamethyl melamine, thiotepa, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase, camptothecin, CPT-11, topotecan, ara-

C, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons and interleukins.

[00160] In certain embodiments, at least one chemical entity chosen from compounds of Formula 1, and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, can be administered in combination with an anti-inflammatory agent. Anti-inflammatory agents include NSAIDs, non-specific and COX-2 specific cyclooxygenase enzyme inhibitors, gold-containing compounds, corticosteroids, methotrexate, tumor necrosis factor receptor (TNF) receptors antagonists, immunosuppressants and methotrexate. Examples of NSAIDs include ibuprofen, flurbiprofen, naproxen and naproxen sodium, diclofenac, combinations of diclofenac sodium and misoprostol, sulindac, oxaprozin, diflunisal, piroxicam, indomethacin, etodolac, fenoprofen calcium, ketoprofen, sodium nabumetone, sulfasalazine, tolmetin sodium, and hydroxychloroquine. Examples of NSAIDs also include COX-2 specific inhibitors (i.e., a compound that inhibits COX-2 with an IC_{50} that is at least 50-fold lower than the IC_{50} for COX-1) such as celecoxib, valdecoxib, lumiracoxib, etoricoxib and/or rofecoxib. In certain embodiments, the anti-inflammatory agent can be a salicylate. Salicylates include acetylsalicylic acid or aspirin, sodium salicylate, and choline and magnesium salicylates. The anti-inflammatory agent can also be a corticosteroid. For example, the corticosteroid may be cortisone, dexamethasone, methylprednisolone, prednisolone, prednisolone sodium phosphate, and prednisone. In certain embodiments, the anti-inflammatory agent can be a gold-containing compound such as gold, sodium thiomalate or auranofin. In certain embodiments, the anti-inflammatory agent can be a metabolic inhibitor such as a dihydrofolate reductase inhibitor, such as methotrexate or a dihydroorotate dehydrogenase inhibitor, such as leflunomide. Certain embodiments of the present disclosure include combinations in which at least one anti-inflammatory compound can be an anti-C5 monoclonal antibody (such as eculizumab or pexelizumab), a TNF antagonist, such as entanercept, or infliximab, which is an anti-TNF alpha monoclonal antibody, and combinations in which at least one active agent is an immunosuppressant compound such as methotrexate, leflunomide, cyclosporine, tacrolimus, azathioprine, or mycophenolate mofetil.

[00161] Dosage levels of the order of from 0.1 mg to 140 mg per kilogram, such as from 1 to 50 mg per kilogram, of body weight per day can be useful in the treatment of the above- indicated conditions (0.5 mg to 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage

unit forms will generally contain from 1 mg to 500 mg of an active ingredient.

[00162] Frequency of dosage may also vary depending on the compound used and the particular disease treated. In certain embodiments, a dosage regimen of 4 times daily or less is used. In certain embodiments, a dosage regimen of 1 or 2 times daily is used.

[00163] It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease in the patient undergoing therapy.

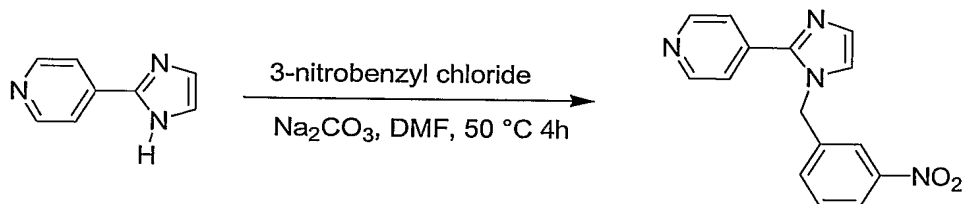
EXAMPLES

[00164] The invention is further illustrated by the following non-limiting examples.

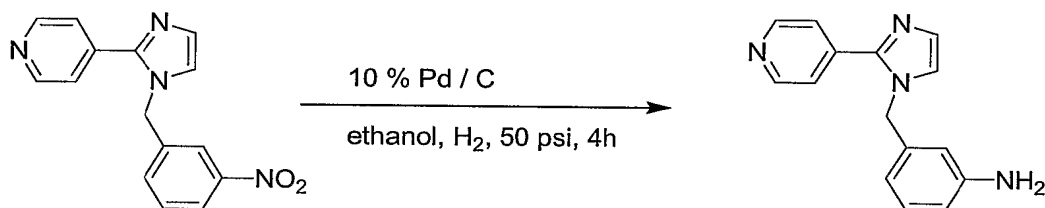
[00165] In the examples below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

DME	=	dimethyl ether
DMEM	=	Dulbecco's modified Eagle's medium
DMF	=	N,N-dimethylformamide
DMSO	=	dimethylsulfoxide
g	=	gram
h	=	hour
mg	=	milligram
min	=	minutes
mL	=	milliliter
mmol	=	millimoles
mM	=	millimolar
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nm	=	nanometer
nM	=	nanomolar
PBS	=	phosphate buffered saline
μ L	=	microliter
μ M	=	micromolar

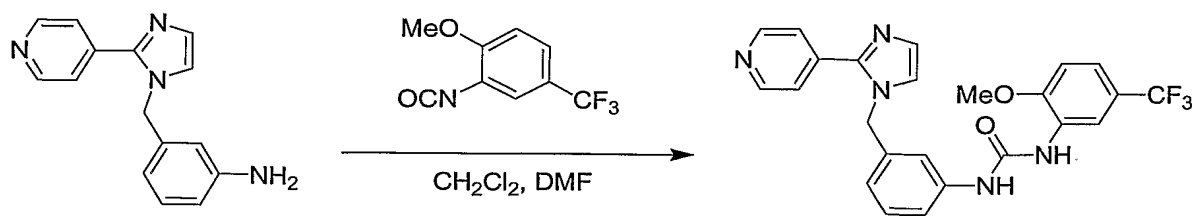
EXAMPLE 1.



[00166] 4-[1-(3-Nitro-benzyl)-1H-imidazol-2-yl]-pyridine: DMF (20 mL) is added to 4-(1H-Imidazol-2-yl)-pyridine (930 mg, 6.4 mmol), sodium carbonate (1.92 g, 20 mmol), and 3-nitrobenzyl chloride (1.71 g, 10 mmol) and the mixture is warmed to $50\text{ }^\circ\text{C}$ for 4h. Water (100 mL) is added and the corresponding mixture is extracted with EtOAc (100 mL), dried over anhydrous sodium sulfate, and crude solution is concentrated under reduced pressure. The organics are dissolved in DCM and filtered through a plug of silica eluting first with DCM, and then washing with 20% MeOH : 80% DCM to afford 4-[1-(3-Nitro-benzyl)-1H-imidazol-2-yl]-pyridine as an off-white solid.

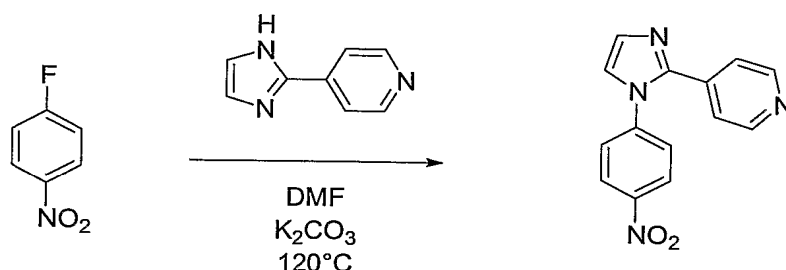


[00167] 3-(2-Pyridin-4-yl-imidazol-1-ylmethyl)-phenylamine: Ethanol (20 mL) is added to 4-[1-(3-Nitro-benzyl)-1H-imidazol-2-yl]-pyridine (730 mg, 2.6 mmol) and 10% palladium on charcoal (100 mg) under an atmosphere of argon. The atmosphere is purged 3 times with H_2 on a Parr shaker type hydrogenation apparatus, and the mixture is shaken for 4 h at 50 psi H_2 . The mixture is filtered through celite, and the filter pad is washed with DCM and MeOH (1:1). The solution was concentrated under reduced pressure to afford 3-(2-Pyridin-4-yl-imidazol-1-ylmethyl)-phenylamine as an off-white solid.

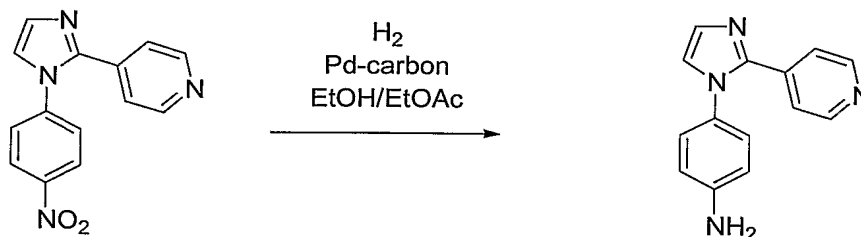


[00168] **1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea:** To a solution of 3-(2-Pyridin-4-yl-imidazol-1-ylmethyl)-phenylamine (50 mg, 0.2 mmol) in DCM (4.0 mL) and DMF (1.0 mL) is added 2-isocyanato-1-methoxy-4-trifluoromethyl-benzene (43 mg, 0.2 mmol) and allowed to react overnight. The resulting crude was concentrated under reduced pressure and the residue is purified by column chromatography (DCM:MeOH) to afford 1-(2-methoxy-5-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea as a white solid.

EXAMPLE 2

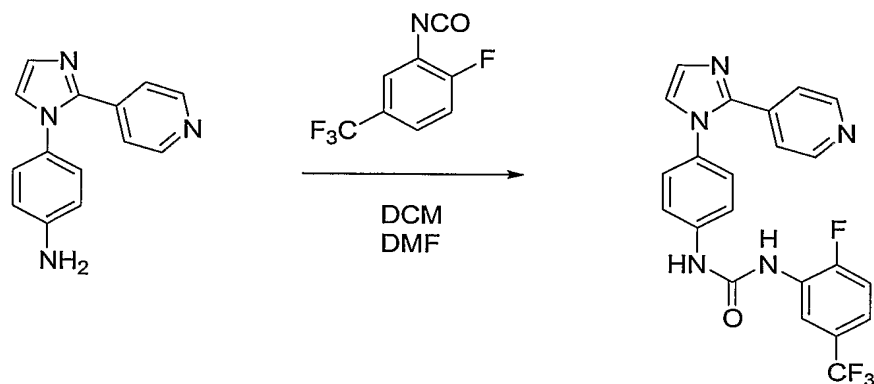


[00169] **4-[1-(4-Nitro-phenyl)-1H-imidazol-2-yl]-pyridine:** 1-Fluoro-4-nitro-benzene (80.2 g, 0.57 mmol) is dissolved in DMF (550 mL) and to that solution is added K₂CO₃ (157.0 g, 1.14 mmol). To that solution is added 4-(1H-imidazol-2-yl)-pyridine (55.0 g, 0.38 mmol) and the reaction is heated at 100°C for 18 h. The solution is then cooled to RT and EtOAc (1.5 L) and water (2.0 L) are then added and the suspension is vacuum filtered. The resulting solid was then purified by column chromatography (EtOAc) to afford 4-[1-(4-nitro-phenyl)-1H-imidazol-2-yl]-pyridine as a brown solid.



[00170] **4-(2-Pyridin-4-yl-imidazol-1-yl)-phenylamine:** To a solution of 4-[1-(4-Nitro-phenyl)-1H-imidazol-2-yl]-pyridine (6.16 g, 23.0 mmol) in EtOH (75.0 mL) and 2N HCl (7.0 mL) is added iron powder (325 mesh, 17.40 g, 312 mmol) and refluxed for 1 h. The

solution is then cooled to RT and Na_2CO_3 (4.87 g, 56.0 mmol) is added and the resultant suspension is filtered through a pad of celite (521). The filter cake is then washed with EtOH (100 mL) and the filtrate is concentrated under reduced pressure to a brown solid. The crude sample is then purified by column chromatography (5% MeOH : 95% DCM) to afford 4-(2-Pyridin-4-yl-imidazol-1-yl)-phenylamine as a tan solid.



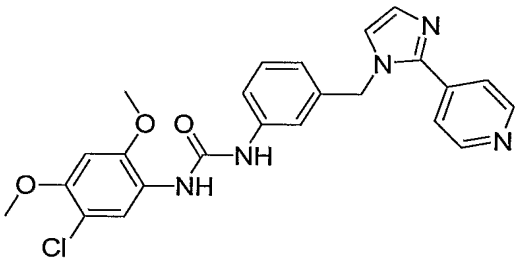
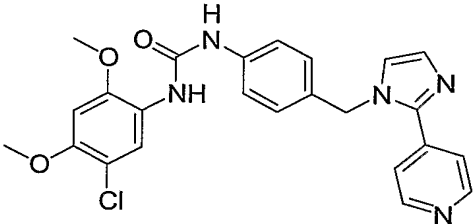
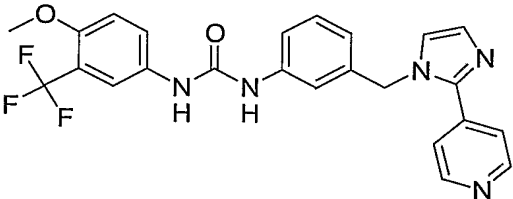
[00171] 1-(2-Fluoro-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea: To a solution of 4-(2-Pyridin-4-yl-imidazol-1-yl)-phenylamine (100 mg, 0.424 mmol) in DCM (4.0 mL) and DMF (1.0 mL) is added 1-fluoro-2-isocyanato-4-trifluoromethyl-benzene (91 mg, 0.445 mmol, 1.05 equiv) and allowed to stir for 2 h at RT. All solvent is then removed under reduced pressure and the resulting solid was purified by column chromatography (5% MeOH : 95% DCM) to afford 1-(2-Fluoro-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea as an off-white solid.

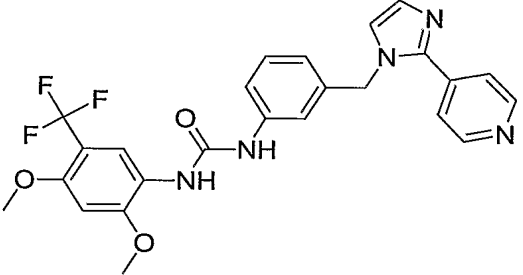
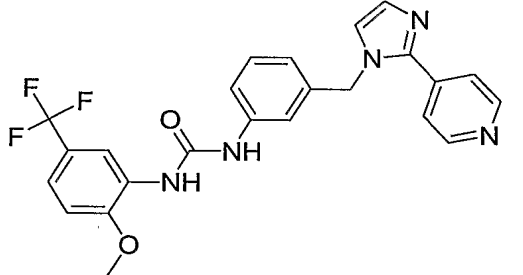
EXAMPLE 3

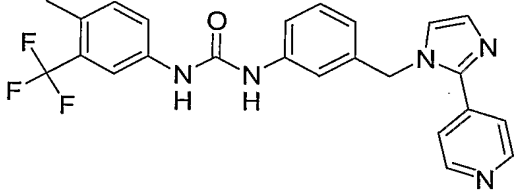
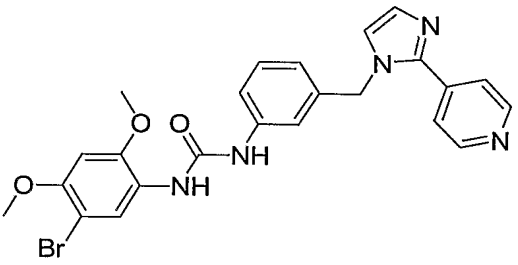
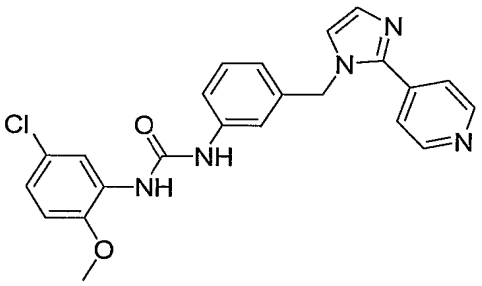
[00172] The following compounds were prepared using procedures similar to those described above. Those of ordinary skill in the art of organic synthesis will recognize when starting materials or reaction conditions should be varied to obtain the desired compound.

[00173] MS data reported in this example was obtained as follows:

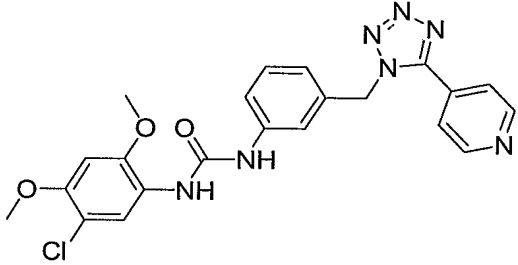
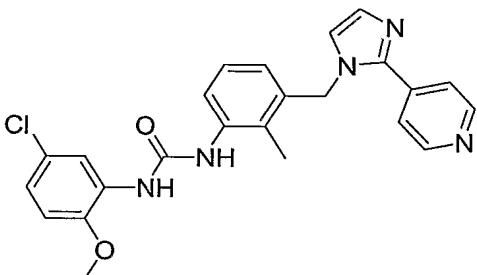
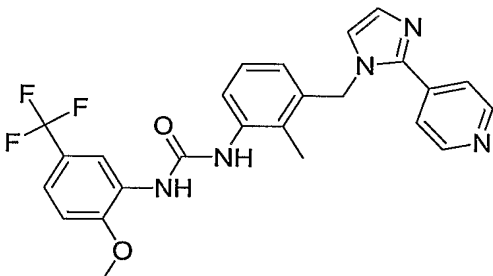
MS conditions: Electrospray MS is performed on a MICROMASS LCT equipped with a LockSpray source for accurate mass measurements. Spectra are acquired in positive ion mode from 100-1000 Da at an acquisition rate of 1 spectrum/0.9s with a 0.1s interscan delay. The instrument is tuned for a resolution of 5000 (FWHM). Every 5th scan is taken from the reference position of the Lockspray source. Leucine enkephalin (556.2771 $[\text{M}+\text{H}]^+$) is used as the reference, or lock mass.

Structure	Name MF MW MS m/z	[M + H]
	<p>1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea</p> <p>C₂₄H₂₂ClN₅O₃</p> <p>463.14</p>	464.33
	<p>1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea</p> <p>C₂₄H₂₂ClN₅O₃</p> <p>463.14</p>	464.13
	<p>1-(4-Methoxy-3-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea</p>	468.43

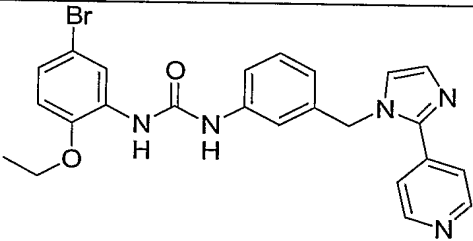
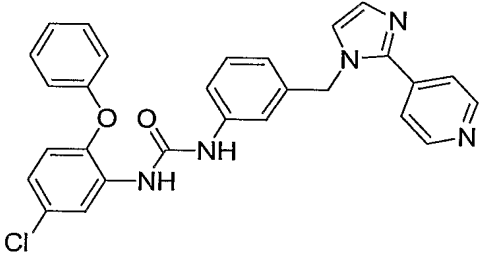
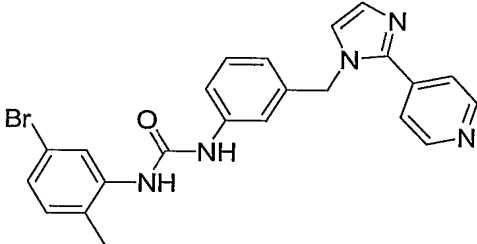
Structure	Name MF MW MS m/z	[M + H]
	C ₂₄ H ₂₀ F ₃ N ₅ O ₂ 467.16	
	1-(2,4-Dimethoxy-5-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea C ₂₅ H ₂₂ F ₃ N ₅ O ₃ 497.17	498.38
	1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea C ₂₄ H ₂₀ F ₃ N ₅ O ₂ 467.16	468.36
	1-(4-Methyl-3-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-	452.32

Structure	Name MF MW MS m/z	[M + H]
	1-(5-(trifluoromethyl)-2-(3-(2-pyridin-4-yl)imidazol-1-ylmethyl)phenyl)- urea C ₂₄ H ₂₀ F ₃ N ₅ O 451.16	
	1-(5-Bromo-2,4-dimethoxy-phenyl)-3- [3-(2-pyridin-4-yl-imidazol-1-ylmethyl)- phenyl]-urea C ₂₄ H ₂₂ BrN ₅ O ₃ 507.09	508.14
	1-(5-Chloro-2-methoxy-phenyl)-3-[3- (2-pyridin-4-yl-imidazol-1-ylmethyl)- phenyl]-urea C ₂₃ H ₂₀ ClN ₅ O ₂ 433.13	434.11

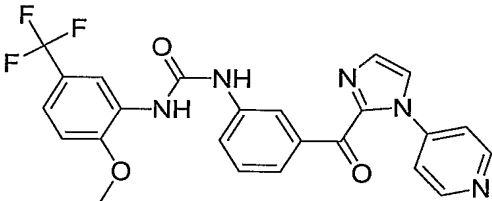
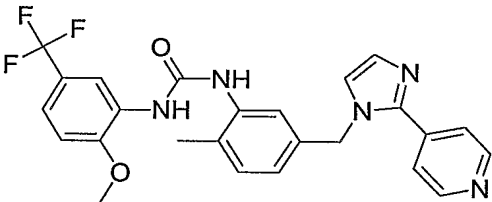
Structure	Name MF MW MS m/z	[M + H]
	<p>1-(2-Fluoro-5-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea</p> <p>C₂₃H₁₇F₄N₅O</p> <p>455.14</p>	456.17
	<p>1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-thiourea</p> <p>C₂₄H₂₂ClN₅O₂S</p> <p>479.12</p>	480.09
	<p>1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[3-(5-pyridin-4-yl-tetrazol-1-ylmethyl)-</p>	466.09

Structure	Name MF MW MS m/z	[M + H]
	phenyl]-urea <chem>C22H20ClN7O3</chem> 465.13	
	1-(5-Chloro-2-methoxy-phenyl)-3-[2-methyl-3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea <chem>C24H22ClN5O2</chem> 447.15	448.10
	1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[2-methyl-3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea <chem>C25H22F3N5O2</chem>	482.07

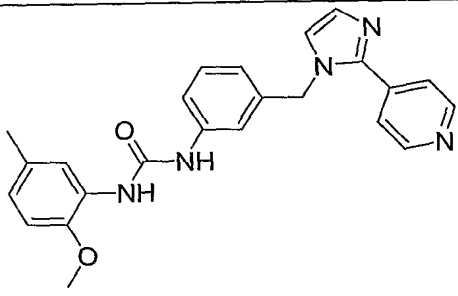
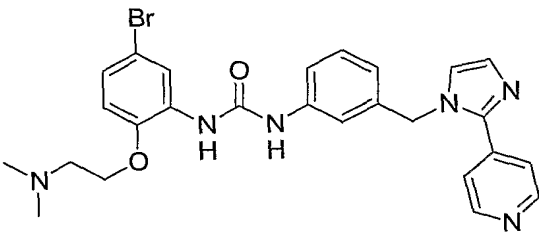
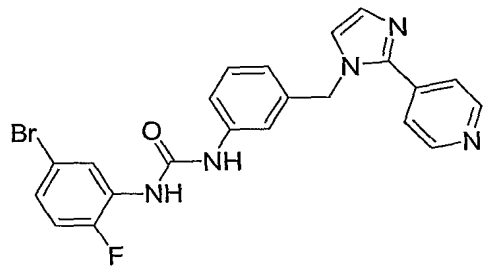
Structure	Name MF MW MS m/z	[M + H]
	481.17	
	<p>1-(5-Bromo-2-methoxy-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea</p> <p>C₂₃H₂₀BrN₅O₂</p> <p>477.08</p>	478.17
	<p>1-(2-Ethoxy-5-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea</p> <p>C₂₅H₂₂F₃N₅O₂</p> <p>481.17</p>	482.07
	<p>1-(5-Bromo-2-ethoxy-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-</p>	492.06

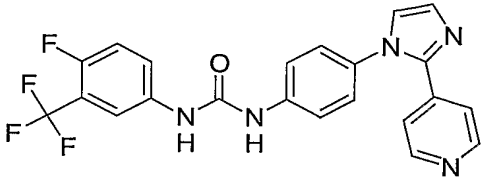
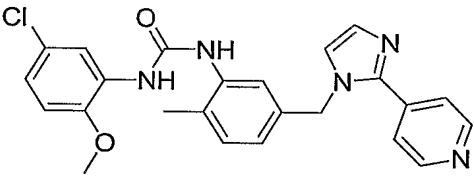
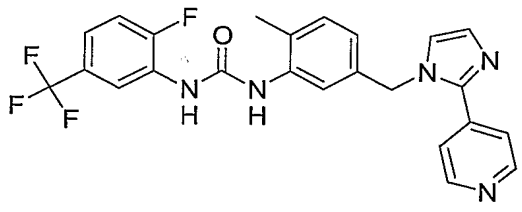
Structure	Name MF MW MS m/z	[M + H]
	1-(5-bromo-2-ethoxyphenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea C ₂₄ H ₂₂ BrN ₅ O ₂ 491.10	
	1-(5-Chloro-2-phenoxy-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea C ₂₈ H ₂₂ ClN ₅ O ₂ 495.15	496.08
	1-(5-Bromo-2-methyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea C ₂₃ H ₂₀ BrN ₅ O 461.09	462.05

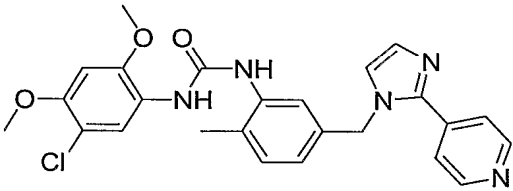
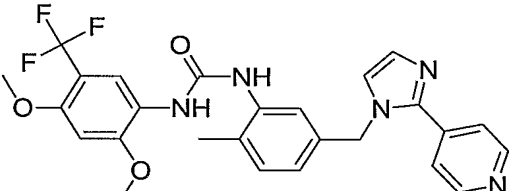
Structure	Name MF MW MS m/z	[M + H]
	<p>1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[4-methyl-3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea</p> <p>C₂₅H₂₂F₃N₅O₂</p> <p>481.17</p>	482.20
	<p>1-(5-Chloro-2-methyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea</p> <p>C₂₃H₂₀ClN₅O</p> <p>417.14</p>	418.13
	<p>1-(2-Chloro-5-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-</p>	472.08

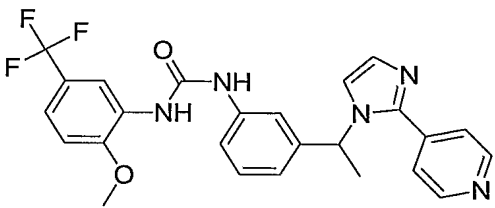
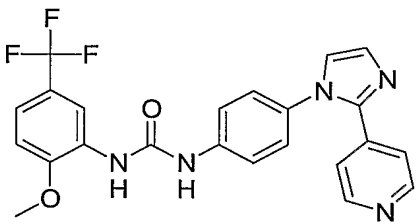
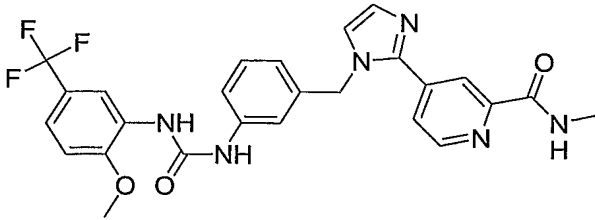
Structure	Name MF MW MS m/z	[M + H]
	urea C23H17ClF3N5O 471.11	
	1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[3-(1-pyridin-4-yl-1H-imidazole-2-carbonyl)-phenyl]-urea C24H18F3N5O3 481.14	482.04
	1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[2-methyl-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea C25H22F3N5O2 481.17	482.05

Structure	Name MF MW MS m/z	[M + H]
	<p>1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[3-(4-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea</p> <p>C₂₄H₂₀F₃N₅O₂</p> <p>467.16</p>	468.05
	<p>1-(2-Methyl-5-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea</p> <p>C₂₄H₂₀F₃N₅O</p> <p>451.16</p>	452.06
	<p>1-(2-Methoxy-5-methyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea</p>	414.11

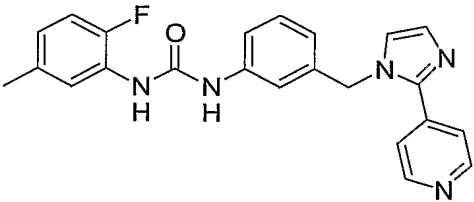
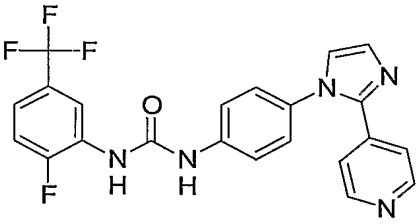
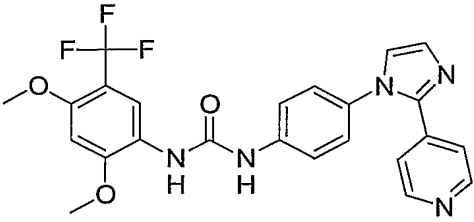
Structure	Name MF MW MS m/z	[M + H]
	C ₂₄ H ₂₃ N ₅ O ₂ 413.19	
	1-[5-Bromo-2-(2-dimethylaminoethoxy)-phenyl]-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea C ₂₆ H ₂₇ BrN ₆ O ₂ 534.14	535.12
	1-(5-Bromo-2-fluorophenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea C ₂₂ H ₁₇ BrFN ₅ O 465.06	465.88

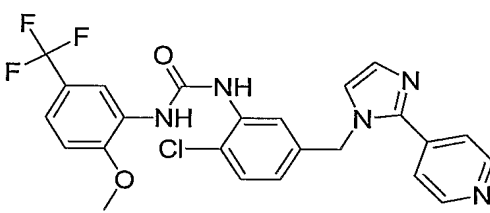
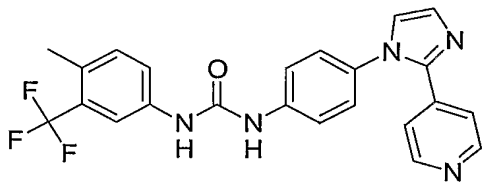
Structure	Name MF MW MS m/z	[M + H]
	1-(4-Fluoro-3-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea C ₂₂ H ₁₅ F ₄ N ₅ O 441.38	442.06
	1-(5-Chloro-2-methoxy-phenyl)-3-[2-methyl-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea C ₂₄ H ₂₂ ClN ₅ O ₂ 447.15	447.96
	1-(2-Fluoro-5-trifluoromethyl-phenyl)-3-[2-methyl-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea 469.92	469.92

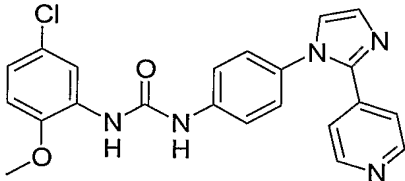
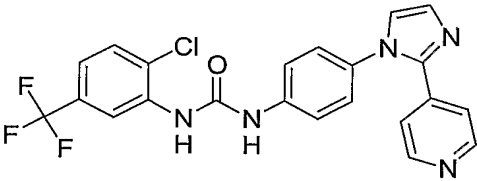
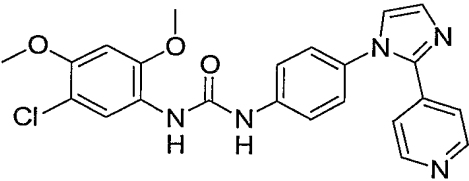
Structure	Name MF MW MS m/z	[M + H]
	phenyl]-urea C24H19F4N5O 469.15	
	1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[2-methyl-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea C25H24ClN5O3 477.16	477.94
	1-(2,4-Dimethoxy-5-trifluoromethyl-phenyl)-3-[2-methyl-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea C26H24F3N5O3 511.18	511.93
		482.15

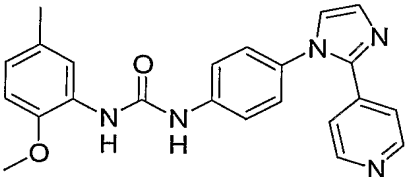
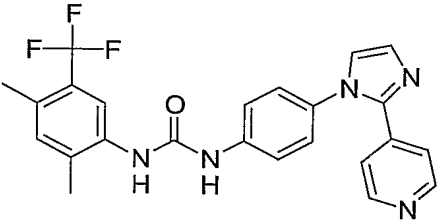
Structure	Name MF MW MS m/z	[M + H]
	<p>1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-{3-[1-(2-pyridin-4-yl-imidazol-1-yl)-ethyl]-phenyl}-urea</p> <p>C₂₅H₂₂F₃N₅O₂</p> <p>481.17</p>	
	<p>1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea</p> <p>C₂₃H₁₈F₃N₅O₂</p> <p>453.14</p>	454.11
	<p>4-(1-{3-[3-(2-Methoxy-5-trifluoromethyl-phenyl)-ureido]-benzyl}-1H-imidazol-2-yl)-pyridine-2-carboxylic acid methylamide</p>	525.16

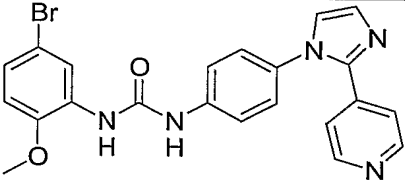
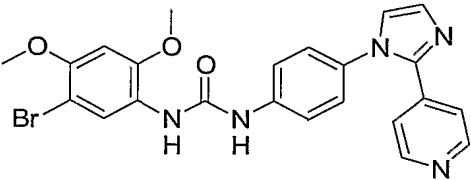
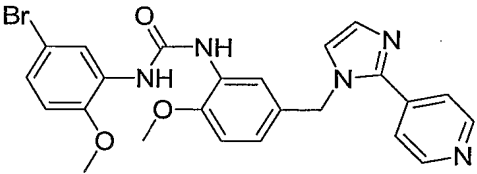
Structure	Name MF MW MS m/z	[M + H]
	C ₂₆ H ₂₃ F ₃ N ₆ O ₃ 524.18	
	1-(5-Bromo-2-methoxy-phenyl)-3-[2-methyl-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea C ₂₄ H ₂₂ BrN ₅ O ₂ 491.10	492.10
	1-(5-Chloro-2-fluoro-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea C ₂₂ H ₁₇ ClF ₂ N ₅ O 421.11	422.09
		402.12

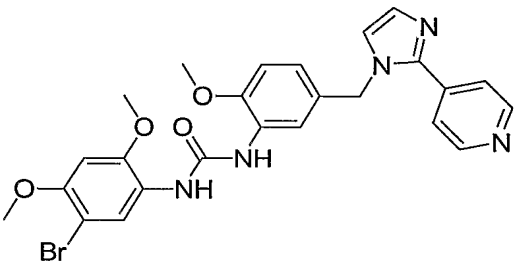
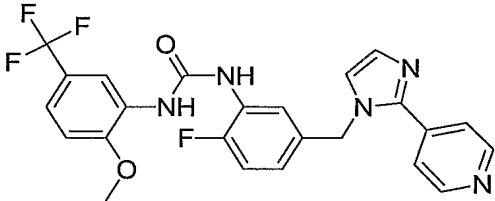
Structure	Name MF MW MS m/z	[M + H]
	<p>1-(2-Fluoro-5-methylphenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea</p> <p>C₂₃H₂₀FN₅O</p> <p>401.17</p>	
	<p>1-(2-Fluoro-5-trifluoromethylphenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea</p> <p>C₂₂H₁₅F₄N₅O</p> <p>441.12</p>	442.06
	<p>1-(2,4-Dimethoxy-5-trifluoromethylphenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea</p>	484.09

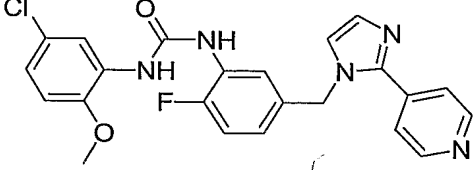
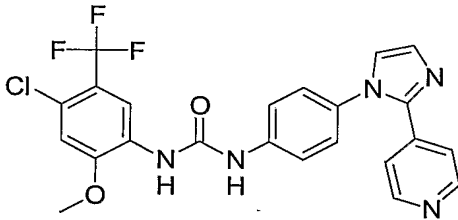
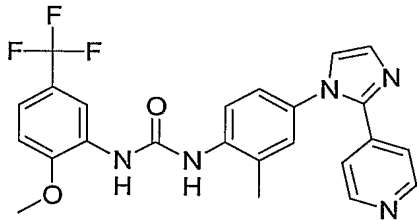
Structure	Name MF MW MS m/z	[M + H]
	C ₂₄ H ₂₀ F ₃ N ₅ O ₃ 483.15	
	1-[2-Chloro-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea C ₂₄ H ₁₉ ClF ₃ N ₅ O ₂ 501.12	502.09
	1-(4-Methyl-3-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea C ₂₃ H ₁₈ F ₃ N ₅ O 437.15	438.13
		420.07

Structure	Name MF MW MS m/z	[M + H]
	<p>1-(5-Chloro-2-methoxy-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea</p> <p>C₂₂H₁₈ClN₅O₂</p> <p>419.11</p>	
	<p>1-(2-Chloro-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea</p> <p>C₂₂H₁₅ClF₃N₅O</p> <p>457.09</p>	458.01
	<p>1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea</p> <p>C₂₃H₂₀ClN₅O₃</p>	450.10

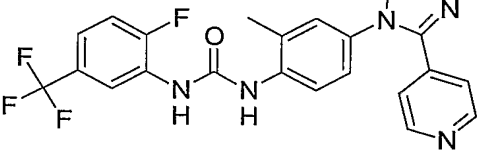
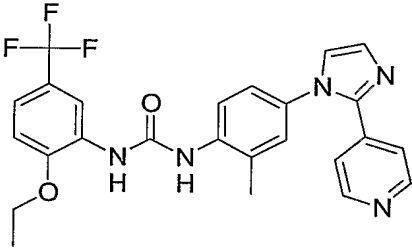
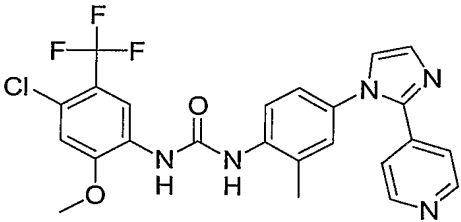
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	449.13	
	<p>1-(2-Methoxy-5-methyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea</p> <p>C₂₃H₂₁N₅O₂</p> <p>399.17</p>	400.11
	<p>1-(2,4-Dimethyl-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea</p> <p>C₂₄H₂₀F₃N₅O</p> <p>451.16</p>	452.10
	1-(5-Bromo-2-	464.15

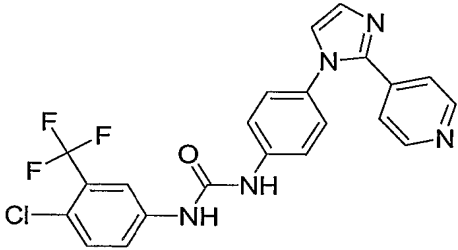
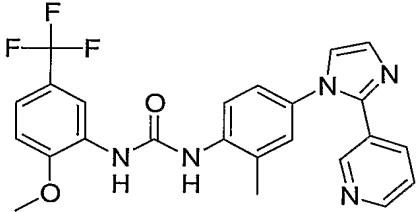
Structure	Name MF MW MS m/z	[M + H]
	methoxy-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea C ₂₂ H ₁₈ BrN ₅ O ₂ 463.06	
	1-(5-Bromo-2,4-dimethoxy-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea C ₂₃ H ₂₀ BrN ₅ O ₃ 493.07	494.08
	1-(5-Bromo-2-methoxy-phenyl)-3-[2-methoxy-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea C ₂₄ H ₂₂ BrN ₅ O ₃	508.12

Structure	Name MF MW MS m/z	[M + H]
	507.09	
	1-(5-Bromo-2,4-dimethoxy-phenyl)-3-[2-methoxy-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea <chem>C25H24BrN5O4</chem> 537.10	538.18
	1-[2-Fluoro-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea <chem>C24H19F4N5O2</chem> 485.15	486.11
	1-(5-Chloro-2-	452.10

Structure	Name MF MW MS m/z	[M + H]
	methoxy-phenyl)-3-[2-fluoro-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea C ₂₃ H ₁₉ ClFN ₅ O ₂ 451.12	
	1-(4-Chloro-2-methoxy-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea C ₂₃ H ₁₇ ClF ₃ N ₅ O ₂ 487.10	488.04
	1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea C ₂₄ H ₂₀ F ₃ N ₅ O ₂	468.06

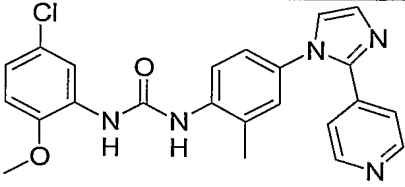
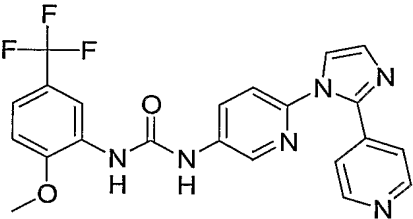
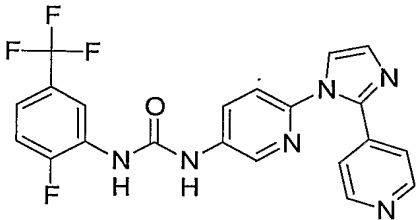
Structure	Name MF MW MS m/z	[M + H]
	467.16	
	<p>1-(5-Bromo-2-methoxy-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea</p> <p>C₂₃H₂₀BrN₅O₂</p> <p>477.08</p>	478.06
	<p>1-(2-Methoxy-4-methyl-5-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea</p> <p>C₂₅H₂₂F₃N₅O₂</p> <p>481.17</p>	482.01
	<p>1-(2-Fluoro-5-trifluoromethyl-phenyl)-3-[2-methyl-</p>	456.05

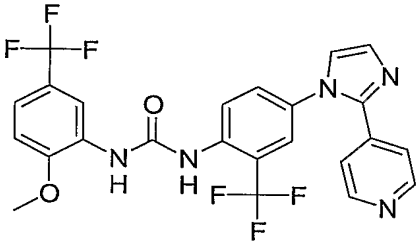
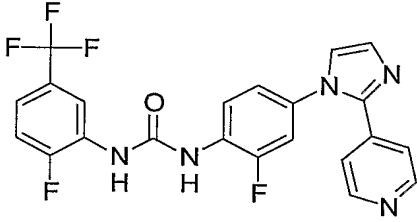
Structure	Name MF MW MS m/z	[M + H]
	4-(2-pyridin-4-yl- imidazol-1-yl)- phenyl]-urea C23H17F4N5O 455.14	
	1-(2-Ethoxy-5- trifluoromethyl- phenyl)-3-[2-methyl- 4-(2-pyridin-4-yl- imidazol-1-yl)- phenyl]-urea C25H22F3N5O2 481.17	482.01
	1-(4-Chloro-2- methoxy-5- trifluoromethyl- phenyl)-3-[2-methyl- 4-(2-pyridin-4-yl- imidazol-1-yl)-phenyl] -urea	502.00

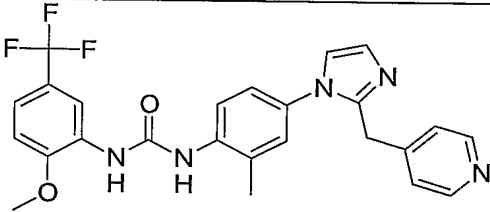
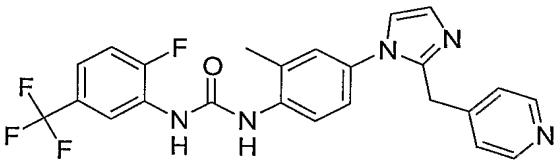
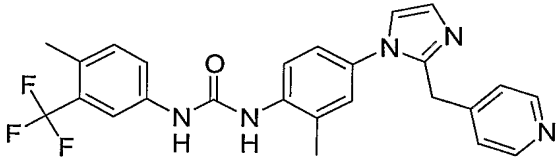
Structure	Name MF MW MS m/z	[M + H]
	C ₂₄ H ₁₉ ClF ₃ N ₅ O ₂ 501.12	
	1-(4-Chloro-3-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea C ₂₂ H ₁₅ ClF ₃ N ₅ O 457.09	458.03
	1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-3-yl-imidazol-1-yl)-phenyl]-urea C ₂₄ H ₂₀ F ₃ N ₅ O ₂ 467.16	468.01
	1-(4-Methoxy-3-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-	468.13

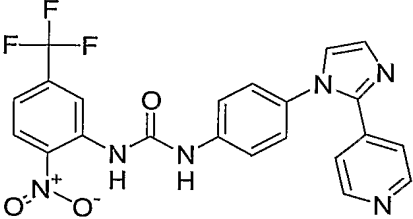
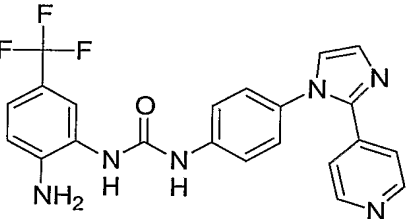
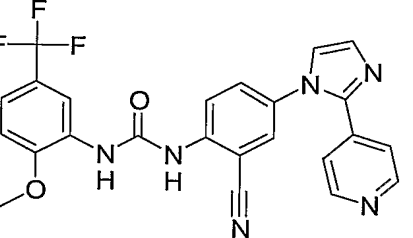
Structure	Name MF MW MS m/z	[M + H]
	imidazol-1-yl)- phenyl]-urea <chem>C24H20F3N5O2</chem> 467.16	
	1-(4-Chloro-3- trifluoromethyl- phenyl)-3-[2-methyl- 4-(2-pyridin-4-yl- imidazol-1-yl)- phenyl]-urea <chem>C23H17ClF3N5O</chem> 471.11	472.11
	1-(4-Fluoro-3- trifluoromethyl- phenyl)-3-[2-methyl- 4-(2-pyridin-4-yl- imidazol-1-yl)- phenyl]-urea <chem>C23H17F4N5O</chem>	456.05

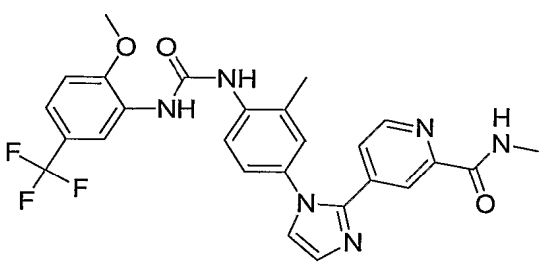
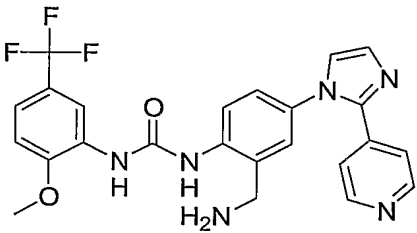
Structure	Name MF MW MS m/z	[M + H]
	455.14	
	1-[2-Methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-3-(4-methyl-3-trifluoromethyl-phenyl)-urea C ₂₄ H ₂₀ F ₃ N ₅ O 451.16	452.06
	1-(5-Bromo-2-ethoxy-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea C ₂₄ H ₂₂ BrN ₅ O ₂ 491.10	492.04
	1-(5-Chloro-2-methoxy-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea C ₂₄ H ₂₂ ClN ₅ O ₂ 434.12	434.12

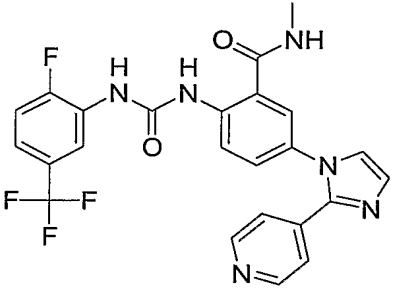
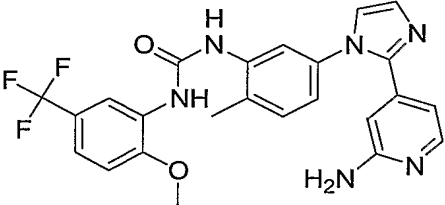
Structure	Name MF MW MS m/z	[M + H]
	yl-imidazol-1-yl)- phenyl]-urea C ₂₃ H ₂₀ ClN ₅ O ₂ 433.13	
	1-(2-Methoxy-5- trifluoromethyl- phenyl)-3-[6-(2- pyridin-4-yl-imidazol- 1-yl)-pyridin-3-yl]- urea C ₂₂ H ₁₇ F ₃ N ₆ O ₂ 454.14	455.12
	1-(2-Fluoro-5- trifluoromethyl- phenyl)-3-[6-(2- pyridin-4-yl-imidazol- 1-yl)-pyridin-3-yl]- urea C ₂₁ H ₁₄ F ₄ N ₆ O 442.12	443.14
		522.27

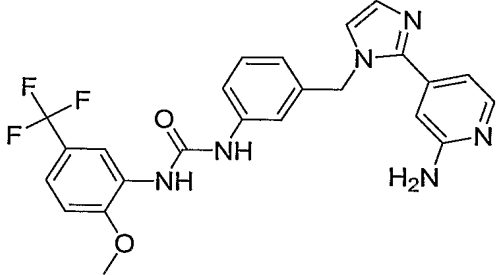
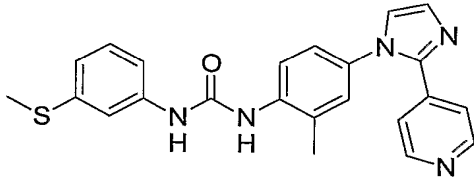
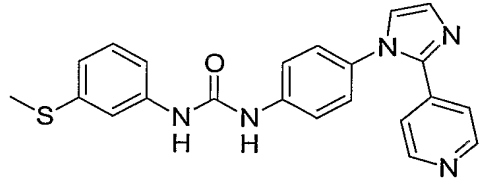
Structure	Name MF MW MS m/z	[M + H]
	<p>1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-2-trifluoromethyl-phenyl]-urea</p> <p>C₂₄H₁₇F₆N₅O₂</p> <p>521.13</p>	
	<p>1-[2-Fluoro-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-3-(2-fluoro-5-trifluoromethyl-phenyl)-urea</p> <p>C₂₂H₁₄F₅N₅O</p> <p>459.11</p>	459.99
	<p>1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-</p>	482.12

Structure	Name MF MW MS m/z	[M + H]
	1-(2-methyl-4-(2-pyridin-4-ylmethyl-imidazol-1-yl)-phenyl)-urea C ₂₅ H ₂₂ F ₃ N ₅ O ₂ 481.17	
	1-(2-Fluoro-5-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-ylmethyl-imidazol-1-yl)-phenyl]-urea C ₂₄ H ₁₉ F ₄ N ₅ O 469.15	470.06
	1-[2-Methyl-4-(2-pyridin-4-ylmethyl-imidazol-1-yl)-phenyl]-3-(4-methyl-3-trifluoromethyl-phenyl)-urea C ₂₅ H ₂₂ F ₃ N ₅ O	466.11

Structure	Name MF MW MS m/z	[M + H]
	<p>1-(2-Nitro-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea</p> <p>C₂₂H₁₅F₃N₆O₃</p> <p>468.12</p>	468.99
	<p>1-(2-Amino-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea</p> <p>C₂₂H₁₇F₃N₆O</p> <p>438.14</p>	439.02
	<p>1-[2-Cyano-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea</p>	479.04

Structure	Name MF MW MS m/z	[M + H]
	C ₂₄ H ₁₇ F ₃ N ₆ O ₂ 478.14	
	<p>4-(1-{4-[3-(2-Methoxy-5-trifluoromethyl-phenyl)-ureido]-3-methyl-phenyl}-1H-imidazol-2-yl)-pyridine-2-carboxylic acid methylamide</p> <p>C₂₆H₂₃F₃N₆O₃</p> <p>524.18</p>	525.03
	<p>1-[2-Aminomethyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea</p> <p>C₂₄H₂₁F₃N₆O₂</p> <p>482.17</p>	483.08

Structure	Name MF MW MS m/z	[M + H]
	<p>2-[3-(2-Fluoro-5-trifluoromethyl-phenyl)-ureido]-N-methyl-5-(2-pyridin-4-yl-imidazol-1-yl)-benzamide</p> <p>C₂₄H₁₈F₄N₆O₂</p> <p>498.14</p>	499.27
	<p>1-{5-[2-(2-Amino-pyridin-4-yl)-imidazol-1-yl]-2-methyl-phenyl}-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea</p> <p>C₂₄H₂₁F₃N₆O₂</p> <p>482.17</p>	483.26
	<p>1-{3-[2-(2-Amino-pyridin-4-yl)-imidazol-1-ylmethyl]-phenyl}-3-(2-methoxy-5-</p>	483.26

Structure	Name MF MW MS m/z	[M + H]
	trifluoromethyl- phenyl)-urea C ₂₄ H ₂₁ F ₃ N ₆ O ₂ 482.17	
	1-[2-Methyl-4-(2- pyridin-4-yl-imidazol- 1-yl)-phenyl]-3-(3- methylsulfanyl- phenyl)-urea C ₂₃ H ₂₁ N ₅ OS 415.15	416.19
	1-(3-Methylsulfanyl- phenyl)-3-[4-(2- pyridin-4-yl-imidazol- 1-yl)-phenyl]-urea C ₂₂ H ₁₉ N ₅ OS 401.13	402.18

EXAMPLE 4. ASSAY FOR EPHB₄ KINASE ACTIVITY

[00174] The following is a procedure for a standard biochemical assay for EphB₄ Kinase Activity that can be used to test compounds disclosed in this application.

Materials:

96-well, ½ area flat bottom, white polystyrene plates are purchased from Costar, cat #3693.

[00175] The cytoplasmic domain of recombinant EphB₄ kinase (amino acids 596-987, *Homo sapiens* EphB₄, GENBANK Accession No. AY056047.1) with a C-terminal V5-(his)₆ tag is purified from Sf9 cells. Purity of >95% is assessed by Sypro-Ruby staining of SDS gels.

[00176] PTK Biotinylated Peptide Substrate 2, is purchased from Promega, cat #V288A.

[00177] LANCE Eu-W1024 labeled anti-phosphotyrosine antibody (PT66) is purchased from Perkin-Elmer, cat #AD0068. Kinase Buffer is purchased from Cell Signaling, cat #9802.

[00178] Dilutions of compounds are made in 100% DMSO at 20X the final desired concentration. Compounds in 100% DMSO are transferred (1.25 µL) to the 96 well assay plate. A 18.75 µL volume of master mix containing the final concentrations (in 25 ul) of 0.01% BSA, 1X Cell Signaling Kinase Buffer, 0.5 µM PTK Biotinylated Peptide Substrate 2, and 18.6 ng/well of EphB₄ kinase is added to all wells, except the four negative control wells (which contain no kinase), and mixed. To initiate the reaction, 5 µL of 550 uM ATP is added to each well. (Final Concentration of ATP = 110 µM). The reactions are incubated for 1 hour at room temperature (RT). After incubation a quantity of 8.35 µL of a 4X SA-APC Detection Mix is added to each well. The final concentration of Eu-labelled PT66 antibody is 1 nM and the SA-APC is 20 nM (based on the SA moiety). The reaction plates are incubated at RT for at least 15 minutes after SA-APC Detection Mix addition. The reaction plates are read on an Envision plate reader (Perkin-Elmer) with 605nm Excitation at 605nm and 640nm Emission wavelengths. Values are corrected for the fluorescence in the absence of enzyme and inhibition curves are fit to the data using a Logit curve-fitting algorithm. IC₅₀ values are determined from these inhibition curves.

EXAMPLE 5. EPHB₄ CELLULAR ASSAY

[00179] The following is a procedure for a standard cell-based assay for EphB₄ kinase

activity that can be used to test compounds disclosed in this application.

[00180] HEK293 cells stably expressing V5-epitope tagged EphB₄ are grown to ~75% confluency, and then incubated for 90 min at 37 °C in low serum media (Optimem) containing test compound. Cells are stimulated for 10 minutes at 37 °C with 500ng/ml EphrinB₂/Fc chimera and 50ng/ml goat-anti-human IgG (FC-specific) in low serum media containing test compound. Cells are washed in ice-cold PBS, lysed, and protein assays are performed on the cleared lysates. Equal protein amounts of each sample are subjected to SDS-PAGE and western blotting with either an anti-phosphotyrosine antibody or an anti-V5 antibody to control for total amounts of V5-epitope-tagged EphB₄ in each lysate.

EXAMPLE 6. BIOCHEMICAL ASSAYS

[00181] The following is a procedure for a standard biochemical assay that can be used to test activity of compounds disclosed herein as inhibitors of c-Kit, VEGFR2, and Tie2 kinase activity.

[00182] Test compounds are diluted 1:20 from an original 200 μ M DMSO stock and incubated with recombinant c-Kit (10 ng), Tie2 (6 ng), or VEGFR2 (1 ng) enzyme (ProQinase GmbH, Germany), biotinylated peptide (PTK peptide 2, Promega) in Cell Signalling kinase buffer (c-Kit and Tie2) or Upstate Kinase buffer (VEGFR2) and 5 μ l of ATP (final concentrations: 85 μ M for the VEGFR2 assay, 60 μ M for the Tie2 assay, and 150 μ M for the c-Kit assay) for 60 minutes at room temperature. The final assay volume is 25 μ l. After incubation a detection Mix, which includes 1 nM LANCE Eu-W1024 labeled anti-phosphotyrosine antibody PT66 (Perkin-Elmer, cat #AD0068) and 20 nM SA-APC (based on the SA moiety), is added. The reaction plates are incubated at room temperature for at least 15 minutes after SA-APC detection mix addition. The reaction plates are then read on an Envision plate reader (Perkin-Elmer) with 605nm excitation 615 nM and 640nm emission wavelengths.

[00183] For a negative control, i.e. a readout in which the kinases are not inhibited, the assay is run without any test compound added. Staurosporine, a general kinase inhibitor, is used as a positive control.

[00184] IC₅₀ values are determined from an 11-point saturation binding curve for test compounds that show significant inhibition of one of the tyrosine kinases. In these assays concentration of test compound ranges from 10 μ M to 20nM. Equilibrium binding parameters are determined by fitting the allosteric Hill equation to the measured values with

the aid of the computer program, such as FitP™ (BIOSOFT, Ferguson, MO).

EXAMPLE 7. TEST RESULTS

[00185] Certain compounds described in Examples 1-3 were tested in the assays for EphB₄ kinase activity (as outlined in Examples 4 and 5), and found to exhibit an IC₅₀ of 1 micromolar or less. Certain of those compounds exhibited an IC₅₀ of 500 nM or less in these assays. Certain of those compounds exhibited an IC₅₀ of 50 nM or less in these assays.

[00186] Certain compounds described in Examples 1-3 were tested in the assay for c-Kit kinase activity (as outlined in example 6) and found to exhibit an IC₅₀ of 1 micromolar or less. Certain of those compounds exhibited an IC₅₀ of 500 nM or less in the assay for c-Kit kinase activity. Certain of those compounds exhibited an IC₅₀ of 50 nM or less in this assay.

[00187] Certain compounds described in Examples 1-3 were also tested in the assay for VEGFR2 kinase activity (as outlined in example 6). Certain of those compounds were found to exhibit an IC₅₀ of 1 micromolar or less. Certain of those compounds exhibited an IC₅₀ of 500 nM or less in this assay. Certain of those compounds exhibited an IC₅₀ of 50 nM or less in this assay.

[00188] Certain compounds described in Examples 1-3 were also tested in the assay for Tie2 kinase activity (as outlined in example 6) and found to exhibit an IC₅₀ of 1 micromolar or less. Certain of those compounds exhibited an IC₅₀ of 500 nM or less in this assay. Certain of those compounds exhibited an IC₅₀ of 50 nM or less in this assay.

[00189] Certain compounds described in Examples 1-3 were also tested in the assays described herein and were found to exhibit an IC₅₀ of 1 micromolar or less against two or more kinases chosen from EphB₄, c-Kit, Tie2, and VEGFR2. Certain compounds described in Examples 1-3 were also tested in the assays described herein and were found to exhibit an IC₅₀ of 100 nm or less against two or more kinases chosen from EphB₄, c-Kit, Tie2, and VEGFR2.

[00190] Certain compounds described in Examples 1-3 were also tested in the assays described herein and were found to exhibit an IC₅₀ of 1 micromolar or less against three or more kinases chosen from EphB₄, c-Kit, Tie2, and VEGFR2. Certain compounds described in Examples 1-3 were also tested in the assays described herein and were found to exhibit an IC₅₀ of 100 nm or less against three or more kinases chosen from EphB₄, c-Kit, Tie2, and VEGFR2.

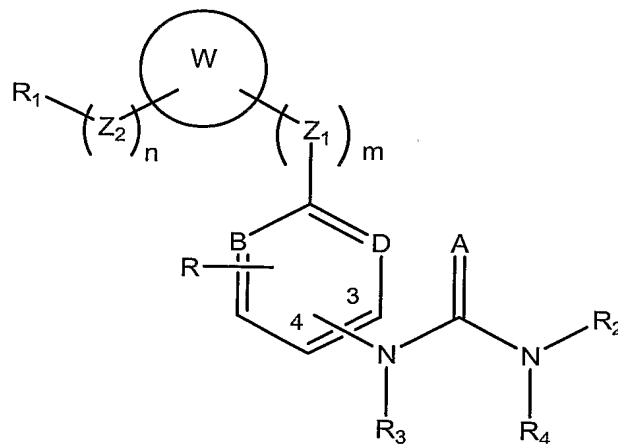
[00191] Certain compounds described in Examples 1-3 were also tested in the assays

described herein and were found to exhibit an IC_{50} of 1 micromolar or less against each of EphB₄, c-Kit, Tie2, and VEGFR2. Certain compounds described in Examples 1-3 were also tested in the assays described herein and were found to exhibit an IC_{50} of 100 nm or less against each of EphB₄, c-Kit, Tie2, and VEGFR2.

[00192] While certain embodiments have been shown and described, various modifications and substitutions may be made thereto without departing from the spirit and scope of the invention. Accordingly, it is to be understood that the present invention has been described by way of illustration and not limitations.

What is claimed is:

1. At least one chemical entity chosen from compounds of Formula 1



(Formula 1)

and pharmaceutically acceptable salts, solvates, crystal forms, chelates, non-covalent complexes, prodrugs, and mixtures thereof, wherein

A is chosen from O and S;

B and D are chosen from CH and N, provided that at least one of B and D is CH;

R represents 0 to 2 substituents independently chosen from hydroxy, nitro, cyano, optionally substituted amino, aminocarbonyl, halo, carboxy, optionally substituted acyl, optionally substituted alkoxy, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, sulfanyl, sulfinyl, sulfonyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycloalkyl;

R₁ is optionally substituted heteroaryl;

W is optionally substituted heteroaryl;

Z₁ is -CR₅R₆- wherein each R₅ and R₆ is independently chosen from hydrogen, optionally substituted C₁-C₆ alkyl, and halo;

m is chosen from 0, 1, and 2;

Z₂ is -CR₇R₈- wherein each R₇ and R₈ is independently chosen from hydrogen, optionally substituted C₁-C₆ alkyl, and halo;

n is chosen from 0, 1, and 2;

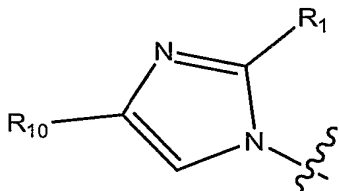
R₂ is optionally substituted aryl; and

R₃ and R₄ are each independently chosen from hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted aryl, and optionally substituted heteroaryl,

provided that

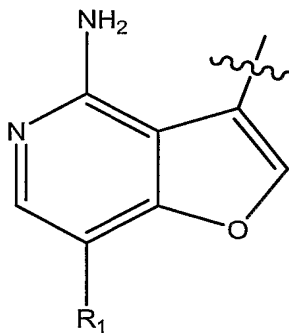
R_1 is not 4-aminothieno[2,3-d]pyrimidine-6-yl when n is 0, m is 0, W is 1-methyl-1H-imidazol-4,5-diyl, A is CH, R is absent, R_3 and R_4 are hydrogen, and R_2 is chosen from phenyl and 2-fluoro-5-(trifluoromethyl)phenyl;

when n is 0, m is 0, A is CH, and R is absent, W is not



where R_{10} is chosen from CF_3 , halo, CN, C_1 - C_8 alkyl, C_1 - C_6 alkenyl; C_3 - C_8 cycloalkyl optionally substituted with a group chosen from hydroxy, cyano, and methoxy, C_1 - C_8 alkoxy; C_1 - C_4 alkyloxyalkyl; C_1 - C_8 alkylthio; C_1 - C_4 alkylthioalkyl; C_1 - C_8 dialkylamino; C_1 - C_4 dialkylaminoalkyl; alkoxycarbonyl optionally substituted with a group chosen from carbocyclyl and heterocyclyl; aryl and heterocyclyl, wherein the aryl and heterocyclyl groups may be optionally substituted with a group chosen from halo, C_1 - C_4 alkyl, C_1 - C_4 alkenyl, CN, dimethylamino, methoxycarbonyl, methoxy, aryl, and heterocyclyl;

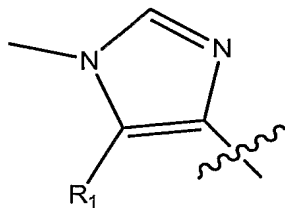
when n is 0, m is 0, A is CH, R is absent, and R_2 is 2-fluoro-5-trifluoromethylphenyl,



W is not

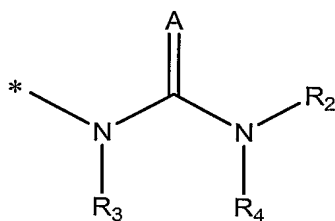
where R_1 is pyridin-3-yl; and

when n is 0, m is 0, A is CH, R is absent, and R_2 is chosen from phenyl and 2-fluoro-5-(trifluoromethyl)phenyl, W is not



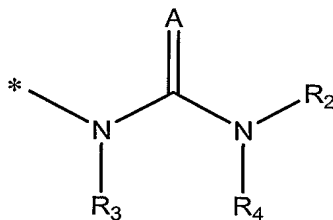
where R_1 is 4-aminoethieno[2,3-d]pyrimidin-6-yl.

2. At least one chemical entity of claim 1 wherein W is chosen from 5- and 6-membered heteroaryl wherein the heteroaryl ring contains at least one nitrogen and optionally includes one, two, or three additional heteroatoms, selected from N, O, and S in the ring.
3. At least one chemical entity of claim 2 wherein W is chosen from pyridyl, pyrazinyl, pyrimidinyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, tetrazolyl, thienyl, furanyl, pyridiziny, triazolyl, and pyrrolyl.
4. At least one chemical entity of claim 3 wherein W is 1H-imidazol-1,2-diyl.
5. At least one chemical entity of any one of claims 1 to 4 wherein the group having the structure:



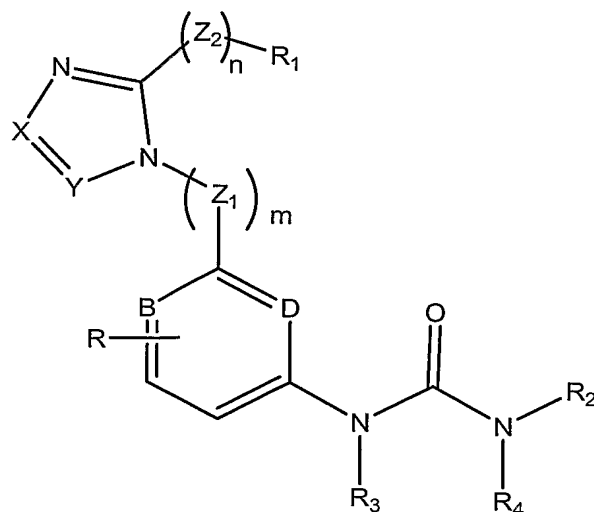
is bonded to the 3-position of the ring wherein A is O.

6. At least one chemical entity of any one of claims 1 to 4 wherein the group having the structure:



is bonded to the 4-position of the ring wherein A is O.

7. At least one chemical entity of claim 1 wherein the compound of Formula 1 is chosen from compounds of Formula 2



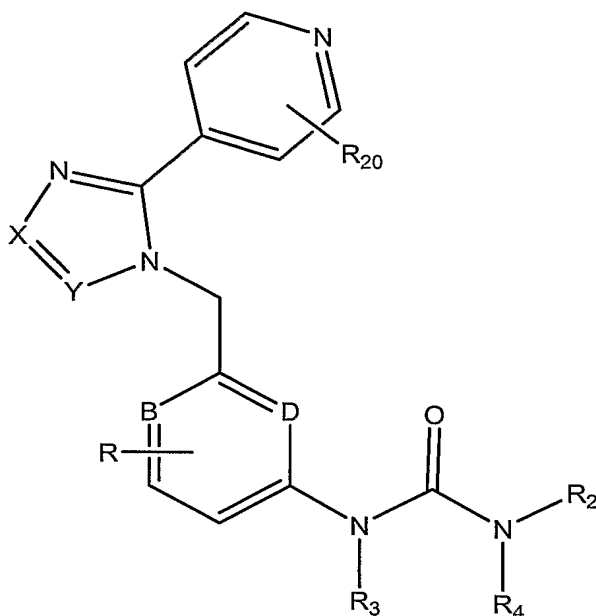
(Formula 2)

wherein

X and Y are independently chosen from CH and N.

8. At least one chemical entity of any one of claims 1 to 7 wherein R_1 is chosen from pyridinyl, and substituted pyridinyl chosen from mono-, di-, and tri-substituted pyridinyls wherein the substituents on the substituted pyridinyl are independently chosen from hydroxy, nitro, cyano, optionally substituted amino, aminocarbonyl, halo, carboxy, optionally substituted acyl, optionally substituted alkoxycarbonyl, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 alkoxy, sulfanyl, sulfinyl, sulfonyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycloalkyl.
9. At least one chemical entity of claim 8 wherein R_1 is chosen from pyridin-4-yl, and substituted pyridin-4-yl chosen from mono-, di-, and tri-substituted pyridin-4-yls and wherein substituents on the substituted pyridin-4-yl are independently chosen from hydroxy, nitro, cyano, optionally substituted amino, aminocarbonyl, halo, carboxy, optionally substituted acyl, optionally substituted alkoxycarbonyl, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 alkoxy, sulfanyl, sulfinyl, sulfonyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycloalkyl.

10. At least one chemical entity of claim 9 wherein the substituents on the substituted pyridin-4-yl are independently chosen from hydroxy, nitro, cyano, optionally substituted amino, halo, carboxy, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆alkoxy, C₁-C₆ alkylsulfanyl, C₁-C₆ acyl, C₁-C₆alkoxycarbonyl, optionally substituted heteroaryl, and heterocycloalkyl.
11. At least one chemical entity of claim 10 wherein the substituents on the substituted pyridin-4-yl are independently chosen from hydroxy, cyano, halo, optionally substituted C₁-C₂ alkyl, and optionally substituted C₁-C₂ alkoxy.
12. At least one chemical entity of claim 9 wherein R₁ is pyridin-4-yl.
13. At least one chemical entity of any one of claims 1 to 12 wherein n is 1 and at least one of R₇ and R₈ is hydrogen.
14. At least one chemical entity of claim 13 wherein R₇ and R₈ are hydrogen.
15. At least one chemical entity of any one of claims 1 to 12 wherein n is 0.
16. At least one chemical entity of any one of claims 1 to 15 wherein m is 1 and at least one of R₅ and R₆ is hydrogen.
17. At least one chemical entity of claim 16 wherein R₅ and R₆ are hydrogen.
18. At least one chemical entity of any one of claims 1 to 15 wherein m is 0.
19. At least one chemical entity of claim 7 wherein the compounds of Formula 2 are chosen from compounds of Formula 3

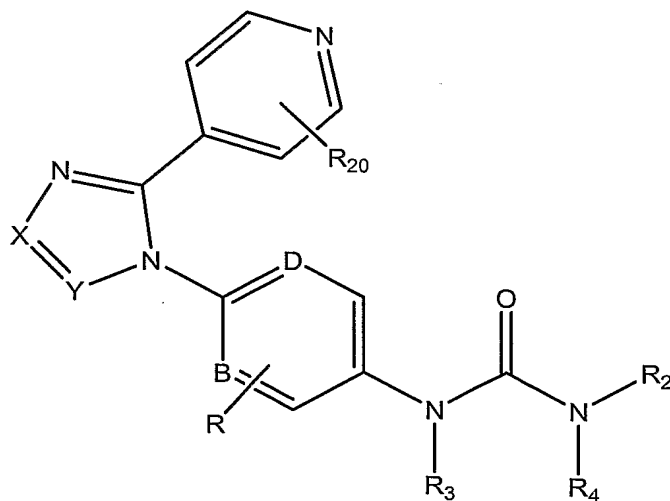


(Formula 3)

wherein

R_{20} represents 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, optionally substituted amino, aminocarbonyl, halo, carboxy, optionally substituted acyl, optionally substituted alkoxycarbonyl, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 alkoxy, sulfanyl, sulfinyl, sulfonyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycloalkyl.

20. At least one chemical entity of claim 7 wherein the compound of Formula 2 is chosen from compounds of Formula 4



(Formula 4)

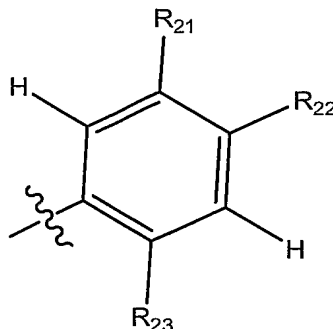
wherein

R₂₀ represents 0 to 3 substituents independently chosen from hydroxy, nitro, cyano, optionally substituted amino, aminocarbonyl, halo, carboxy, optionally substituted acyl, optionally substituted alkoxy, carbonyl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, sulfanyl, sulfinyl, sulfonyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycloalkyl.

21. At least one chemical entity of any one of claims 7 to 20 wherein X and Y are CH.
22. At least one chemical entity of any one of claims 7 to 20 wherein X and Y are N.
23. At least one chemical entity of any one of claim 1 to 22 wherein R₂ is chosen from phenyl, and substituted phenyl chosen from mono-, di-, and tri-substituted phenyls wherein the substituents on the substituted phenyl are independently chosen from hydroxy, nitro, cyano, optionally substituted amino, aminocarbonyl, halo, carboxy, optionally substituted acyl, optionally substituted alkoxy, carbonyl, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted aryloxy, sulfanyl, sulfinyl, sulfonyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycloalkyl.
24. At least one chemical entity of claim 23 wherein the substituents on the substituted phenyl are independently chosen from hydroxy, nitro, cyano, optionally substituted amino, halo, carboxy, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted phenoxy, C₁-C₆ alkylsulfanyl, C₁-C₆ acyl, C₁-C₆ alkoxy, carbonyl, optionally substituted heteroaryl, and heterocycloalkyl.
25. At least one chemical entity of claim 24 wherein the substituents on the substituted phenyl are independently chosen from hydroxy, cyano, halo, optionally substituted C₁-C₂ alkyl, phenoxy, and optionally substituted C₁-C₂ alkoxy.

26. At least one chemical entity of claim 25 wherein the substituents on the substituted phenyl are independently chosen from halo, methyl, methoxy, ethoxy, and trifluoromethyl.

27. At least one chemical entity of any one of claims 1 to 26 wherein R₂ is



wherein

R₂₁ is chosen from hydrogen, halo and optionally substituted lower alkyl;

R₂₂ is chosen from hydrogen, halo, lower alkoxy, and lower alkyl; and

R₂₃ is chosen from hydrogen, lower alkyl, optionally substituted phenoxy, lower alkoxy, and halo.

28. At least one chemical entity of claim 27 wherein R₂₁ is chosen from hydrogen, halo, methyl, and trifluoromethyl.

29. At least one chemical entity of claim 27 or 28 wherein R₂₂ is chosen from hydrogen, halo, methoxy, and methyl.

30. At least one chemical entity of any one of claims 27 to 29 wherein R₂₃ is chosen from hydrogen, methyl, methoxy, ethoxy, and halo.

31. At least one chemical entity of any one of claims claim 19 to 30 wherein R₂₀ is R₂₀ is optionally substituted amino.

32. At least one chemical entity of any one of claims 1 to 31 wherein R₃ and R₄ are each independently chosen from hydrogen and methyl.

33. At least one chemical entity of claim 32 wherein R₃ and R₄ are hydrogen.

34. At least one chemical entity of any one of claims 1 to 33 wherein R represents 1 or 2 substituents independently chosen from halo, C₁-C₂ alkyl, and C₁-C₂ alkoxy.
35. At least one chemical entity of claim 34 wherein R represents 1 or 2 substituents independently chosen from halo, methyl, and methoxy.
36. At least one chemical entity of claim 35 wherein R represents a substituent chosen from halo, methyl, and methoxy.
37. At least one chemical entity of any one of claims 1 to 33 wherein R is absent.
38. At least one chemical entity of any one of claims 1 to 37, wherein the at least one chemical entity exhibits an IC₅₀ of 1 micromolar or less in a standard *in vitro* assay of EphB₄ kinase activity.
39. At least one chemical entity of claim 38, wherein the at least one chemical entity exhibits an IC₅₀ of 500 nanomolar or less in a standard *in vitro* assay of EphB₄ kinase activity.
40. At least one chemical entity of claim 39, wherein the at least one chemical entity exhibits an IC₅₀ of 50 nanomolar or less in a standard *in vitro* assay of EphB₄ kinase activity.
41. At least one chemical entity of any one of claims 1 to 40, wherein the at least one chemical entity exhibits an IC₅₀ of 1 micromolar or less in a standard *in vitro* assay of VEGFR2 kinase activity.
42. At least one chemical entity of claim 41 wherein the at least one chemical entity exhibits an IC₅₀ of 500 nM or less in a standard *in vitro* assay of VEGFR2 kinase activity.
43. At least one chemical entity of claim 42 wherein the at least one chemical entity exhibits an IC₅₀ of 50 nM or less in a standard *in vitro* assay of VEGFR2 kinase activity.

44. At least one chemical entity of any one of claims 1 to 43, wherein the at least one chemical entity exhibits an IC_{50} of 1 micromolar or less in standard *in vitro* assay of Tie2 kinase activity.
45. At least one chemical entity of claim 44, wherein the at least one chemical entity exhibits an IC_{50} of 500 nM or less in a standard *in vitro* assay of Tie2 kinase activity.
46. At least one chemical entity of claim 45, wherein the at least one chemical entity exhibits an IC_{50} of 50 nM or less in a standard *in vitro* assay of Tie2 kinase activity.
47. At least one chemical entity of any one of claims 1 to 46, wherein the at least one chemical entity exhibits an IC_{50} of 1 micromolar or less in a standard *in vitro* assay of c-Kit kinase activity.
48. At least one chemical entity of claim 47, wherein the at least one chemical entity exhibits an IC_{50} of 500 nanomolar or less in a standard *in vitro* assay of c-Kit kinase activity.
49. At least one chemical entity of claim 48, wherein the at least one chemical entity exhibits an IC_{50} of 50 nanomolar or less in a standard *in vitro* assay of c-Kit kinase activity.
50. At least one chemical entity of any one of claims 1 to 37 wherein the at least one chemical entity exhibits an IC_{50} of 1 micromolar or less in a standard *in vitro* assay of EphB₄ kinase activity; an IC_{50} of 1 micromolar or less in a standard *in vitro* assay of VEGFR2 kinase activity; and an IC_{50} of 1 micromolar or less in standard *in vitro* assay of Tie2 kinase activity.
51. At least one chemical entity of claim 1 wherein the compound of Formula 1 is chosen from
- 1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(4-Methoxy-3-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(2,4-Dimethoxy-5-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;

- 1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(4-Methyl-3-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(5-Bromo-2,4-dimethoxy-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(5-Chloro-2-methoxy-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(2-Fluoro-5-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-thiourea;
- 1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[3-(5-pyridin-4-yl-tetrazol-1-ylmethyl)-phenyl]-urea;
- 1-(5-Chloro-2-methoxy-phenyl)-3-[2-methyl-3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[2-methyl-3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(5-Bromo-2-methoxy-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(2-Ethoxy-5-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(5-Bromo-2-ethoxy-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(5-Chloro-2-phenoxy-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(5-Bromo-2-methyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[4-methyl-3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(5-Chloro-2-methyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(2-Chloro-5-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[3-(1-pyridin-4-yl-1H-imidazole-2-carbonyl)-phenyl]-urea;
- 1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[2-methyl-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[3-(4-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(2-Methyl-5-trifluoromethyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;

1-(2-Methoxy-5-methyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-[5-Bromo-2-(2-dimethylamino-ethoxy)-phenyl]-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(5-Bromo-2-fluoro-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(4-Fluoro-3-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
1-(5-Chloro-2-methoxy-phenyl)-3-[2-methyl-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(2-Fluoro-5-trifluoromethyl-phenyl)-3-[2-methyl-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[2-methyl-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(2,4-Dimethoxy-5-trifluoromethyl-phenyl)-3-[2-methyl-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-{3-[1-(2-pyridin-4-yl-imidazol-1-yl)-ethyl]-phenyl}-urea;
1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
4-(1-{3-[3-(2-Methoxy-5-trifluoromethyl-phenyl)-ureido]-benzyl}-1H-imidazol-2-yl)-pyridine-2-carboxylic acid methylamide;
1-(5-Bromo-2-methoxy-phenyl)-3-[2-methyl-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(5-Chloro-2-fluoro-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(2-Fluoro-5-methyl-phenyl)-3-[3-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
1-(2-Fluoro-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
1-(2,4-Dimethoxy-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
1-[2-Chloro-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea;
1-(4-Methyl-3-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
1-(5-Chloro-2-methoxy-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
1-(2-Chloro-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
1-(5-Chloro-2,4-dimethoxy-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
1-(2-Methoxy-5-methyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
1-(2,4-Dimethyl-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
1-(5-Bromo-2-methoxy-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;

- 1-(5-Bromo-2,4-dimethoxy-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(5-Bromo-2-methoxy-phenyl)-3-[2-methoxy-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(5-Bromo-2,4-dimethoxy-phenyl)-3-[2-methoxy-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-[2-Fluoro-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea;
- 1-(5-Chloro-2-methoxy-phenyl)-3-[2-fluoro-5-(2-pyridin-4-yl-imidazol-1-ylmethyl)-phenyl]-urea;
- 1-(4-Chloro-2-methoxy-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(5-Bromo-2-methoxy-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(2-Methoxy-4-methyl-5-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(2-Fluoro-5-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(2-Ethoxy-5-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(4-Chloro-2-methoxy-5-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(4-Chloro-3-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-3-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(4-Methoxy-3-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(4-Chloro-3-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-(4-Fluoro-3-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
- 1-[2-Methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-3-(4-methyl-3-trifluoromethyl-phenyl)-urea;
- 1-(5-Bromo-2-ethoxy-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;

1-(5-Chloro-2-methoxy-phenyl)-3-[2-methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
 1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[6-(2-pyridin-4-yl-imidazol-1-yl)-pyridin-3-yl]-
 urea;
 1-(2-Fluoro-5-trifluoromethyl-phenyl)-3-[6-(2-pyridin-4-yl-imidazol-1-yl)-pyridin-3-yl]-urea;
 1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-2-
 trifluoromethyl-phenyl]-urea;
 1-[2-Fluoro-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-3-(2-fluoro-5-trifluoromethyl-phenyl)-
 urea;
 1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-ylmethyl-imidazol-1-
 yl)-phenyl]-urea;
 1-(2-Fluoro-5-trifluoromethyl-phenyl)-3-[2-methyl-4-(2-pyridin-4-ylmethyl-imidazol-1-yl)-
 phenyl]-urea;
 1-[2-Methyl-4-(2-pyridin-4-ylmethyl-imidazol-1-yl)-phenyl]-3-(4-methyl-3-trifluoromethyl-
 phenyl)-urea;
 1-(2-Nitro-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
 1-(2-Amino-5-trifluoromethyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea;
 1-[2-Cyano-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-3-(2-methoxy-5-trifluoromethyl-
 phenyl)-urea;
 4-(1-{4-[3-(2-Methoxy-5-trifluoromethyl-phenyl)-ureido]-3-methyl-phenyl}-1H-imidazol-2-
 yl)-pyridine-2-carboxylic acid methylamide;
 1-[2-Aminomethyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-3-(2-methoxy-5-
 trifluoromethyl-phenyl)-urea;
 2-[3-(2-Fluoro-5-trifluoromethyl-phenyl)-ureido]-N-methyl-5-(2-pyridin-4-yl-imidazol-1-yl)-
 benzamide;
 1-{5-[2-(2-Amino-pyridin-4-yl)-imidazol-1-yl]-2-methyl-phenyl}-3-(2-methoxy-5-
 trifluoromethyl-phenyl)-urea;
 1-{3-[2-(2-Amino-pyridin-4-yl)-imidazol-1-ylmethyl]-phenyl}-3-(2-methoxy-5-
 trifluoromethyl-phenyl)-urea;
 1-[2-Methyl-4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-3-(3-methylsulfanyl-phenyl)-urea; and
 1-(3-Methylsulfanyl-phenyl)-3-[4-(2-pyridin-4-yl-imidazol-1-yl)-phenyl]-urea.

52. A pharmaceutical composition, comprising at least one chemical entity of any one of claims 1 to 51, together with at least one pharmaceutically acceptable vehicle chosen from carriers, adjuvants, and excipients.

53. A pharmaceutical composition of claim 52, wherein the composition is formulated in a form chosen from injectable fluids, aerosols, creams, gels, tablets, pills, capsules, syrups, ophthalmic solutions, and transdermal patches.

54. A method of treating a patient having a disease or disorder responsive to kinase activity modulation comprising administering to the patient a therapeutically effective amount of at least one chemical entity of any one of claims 1 to 51 or a pharmaceutical composition of claim 52 or 53.

55. The method of claim 54 wherein the patient is a human.

56. The method of claim 54 wherein the patient is chosen from cats and dogs.

57. A method of any one of claims 54 to 56 wherein the disease or disorder responsive to kinase activity modulation is chosen from cancer and diseases characterized by a change in angiogenesis.

58. The method of claim 57, wherein the disease characterized by a change in angiogenesis is chosen from cancerous tumor, macular degeneration, and diabetic retinopathy.

59. The method of any one of claims 54 to 58 wherein the at least one chemical entity is administered by a method chosen from intravenously, intramuscularly, and parenterally.

60. A packaged pharmaceutical composition, comprising the pharmaceutical composition of claim 52 or 53 in a container; and instructions for using the composition to treat a patient suffering from a disease or disorder responsive to kinase activity modulation of one or more tyrosine kinase.

61. The packaged pharmaceutical composition of claim 60 wherein the disease or disorder responsive to kinase activity modulation is chosen from cancer and diseases characterized by a change in angiogenesis.

62. The packaged pharmaceutical composition of claim 61 wherein the disease characterized by a change in angiogenesis is chosen from cancerous tumor, macular degeneration, and diabetic retinopathy.
63. A method of modulating EphB₄ kinase activity, the method comprising contacting cells expressing EphB₄ kinase with at least one chemical entity of any one of claims 38 to 40 in an amount sufficient to detectably inhibit EphB₄ kinase activity *in vitro*.
64. A method of modulating VEGFR2 kinase activity, the method comprising contacting cells expressing VEGFR2 with at least one chemical entity of any one of claims 41 to 43 in an amount sufficient to detectably inhibit VEGFR2 kinase activity *in vitro*.
65. A method of modulating c-Kit kinase activity, the method comprising contacting cells expressing c-Kit with at least one chemical entity of any one of claims 47 to 49 in an amount sufficient to detectably inhibit c-Kit kinase activity *in vitro*.
66. A method of modulating Tie2 kinase activity, the method comprising contacting cells expressing Tie2 with at least one chemical entity of any one of claims 44 to 46 in an amount sufficient to detectably inhibit Tie2 kinase activity *in vitro*.
67. A method of modulating activity of at least one kinase chosen from VEGFR2, EphB₄, Tie2, and c-Kit, the method comprising contacting cells expressing at least one kinase chosen from VEGFR2, EphB₄, Tie2, and c-Kit with at least one chemical entity of any one of claims 1 to 51 in an amount sufficient to detectably inhibit the activity of at least one kinase chosen from VEGFR2, EphB₄, Tie2, and c-Kit *in vitro*.
68. The use of at least one chemical entity for the manufacture of a medicament for the treatment of a patient having a disease responsive to inhibition of at least one kinase chosen from VEGFR2, EphB₄, Tie2, and c-Kit, wherein the at least one chemical entity is a chemical entity of any one of claims 1 to 51.
69. The use of claim 68, wherein the disease responsive to inhibition of at least one kinase is responsive to inhibition of VEGFR2 kinase activity.

70. The use of claim 69, wherein the disease responsive to inhibition of VEGFR2 kinase activity is chosen from cancer and diseases characterized by a change in angiogenesis.
71. The use of claim 70, wherein the diseases characterized by a change in angiogenesis are chosen from cancerous tumor, macular degeneration, and diabetic retinopathy.
72. A method for the manufacture of a medicament for the treatment of a patient having a disease responsive to inhibition of at least one kinase chosen from VEGFR2, EphB₄, Tie2, and c-Kit, comprising including in said medicament at least one chemical entity of any one of claims 1 to 51.
73. The method of claim 72, wherein the disease responsive to inhibition of at least one kinase is responsive to inhibition of VEGFR2 kinase activity.
74. The method of claim 73, wherein the disease responsive to inhibition of VEGFR2 kinase activity is chosen from cancer and diseases characterized by a change in angiogenesis.
75. The method of claim 74, wherein the diseases characterized by a change in angiogenesis are chosen from cancerous tumor, macular degeneration, and diabetic retinopathy.
76. A method for treating a female patient having a female reproductive disorder or condition comprising administering to the female patient a therapeutically effective amount of at least one chemical entity of any one of claims 1 to 51 or a pharmaceutical composition of claim 52 or 53.
77. A method of claim 76 wherein the female reproductive disorder or condition is chosen from endometriosis, endometrial carcinoma, gynecologic bleeding disorders, irregular menstrual cycles, ovulation, premenstrual syndrome (PMS), and menopausal dysfunction.
78. The method of claim 76 or 77 wherein the at least one chemical entity is administered by a method chosen from intravenously, intramuscularly, and parenterally.

79. The method of any of claims 76 to 78 wherein an effective amount of said at least one chemical entity is administered orally.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/001271

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 A61K31/4164 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/072541 A (SMITHKLINE BEECHAM CORPORATION; ADAMS, JERRY, LEROY; KASPAREC, JIRI; S) 4 September 2003 (2003-09-04) examples	1-79
P,A	WO 2005/097755 A (MERCK PATENT GMBH; HOELZEMANN, GUENTER; CRASSIER, HELENE; JONCZYK, ALF) 20 October 2005 (2005-10-20) examples	1-79
A	WO 03/024447 A (SMITHKLINE BEECHAM CORPORATION; HARRIS, PHILIP, ANTHONY; WANG, TONY, Y) 27 March 2003 (2003-03-27) examples	1-79

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

* & * document member of the same patent family

Date of the actual completion of the international search

11 May 2006

Date of mailing of the international search report

26/05/2006

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/001271

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 54-67, 76-79 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/001271

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03072541	A	04-09-2003	AU 2002366440 A1 EP 1436265 A2	09-09-2003 14-07-2004
WO 2005097755	A	20-10-2005	DE 102004015099 A1	20-10-2005
WO 03024447	A	27-03-2003	NONE	